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THE TREATMENT OF ADDISON'S DISEASE BY THE IMPLANTATION METHOD *

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THE implantation of normal suprarenal glands or a potent extract of normal suprarenal glands has been foreshadowed since Addison's disease was first put on a sound clinicopathological basis in 1855. At that time, in his search for an explanation of idiopathic anemia, Thomas Addison as he said "stumbled upon the curious facts" that some asthenic patients of "dingy hue" were found at postmortem examination to have but one demonstrable pathological lesion and that was the destruction of the suprarenal capsules. Obviously he concluded that some significant relationship exists between the clinical syndrome and the pathological changes which he had so accurately observed. Thus and then was laid the first of the pillars upon which the scientific superstructure of replacement therapy of the endocrine glands has been erected.

So far, gland grafting, though rational and sound theoretically, has met only with failure when applied to the correction of suprarenal deficiency disease. Consequently, hope has been directed toward, first, gland extracts; second, isolation of, or synthesis of, a potent hormone or hormones; and third, the implantation of compressed pellets of crystalline hormone compositions. However, the early adumbration of such a practical procedure remained untested and unverified for 75 years; when Hartman, MacArthur and Hartman,[1] Rogoff and Stewart,[2] and Swingle and Pfiffner,[3] working in separate groups and entirely independently, were all able to extract a substance which when injected into bilaterally adrenalectomized animals, manifested life-prolonging powers. These substances were soon purified, roughly standardized biologically, and submitted for clinical assay. Rowntree [4] and others were convinced early that they possess a real therapeutic value. They are now marketed under an approved nomenclature acceptable to the Council

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of Pharmacy and Chemistry of the American Medical Association [5] as follows:

"Adrenal Cortex Extract, Upjohn
Adrenal Cortex Extract, Wilson Laboratories
Cortin, Roche-Organon
Eschatin, Parke-Davis"

It is specified by the Council that as evidence of their standard of strength 1 c.c. of the solution represents the extract derived from 40 grams of fresh gland. That and that alone is the evidence of their potency.

There is no doubt that these extracts contain the hormone or hormones that are necessary for life. Nor is there doubt that, when given in adequate amounts and at adequate intervals of frequency, they have the power to prolong the life of patients suffering from uncomplicated Addison's disease and to cure the crises arising from complications. Besides, they have the merit of being *safe* products and can, therefore, be used by any physician under any ordinary circumstance of practice. No bona fide case of overdosage has ever been recorded.

However, they have some clinical drawbacks. For instance, their potency has not been proved to be constant. This is not unexpected for, as Thorn [6] points out, their activity depends both qualitatively and quantitatively upon the presence of a number of steroid compounds (15 or 20 have been recovered from the suprarenal cortex) and the relative amounts of each steroid compound in a given batch of the extract. Since the only guarantee of potency is that 1 c.c. of the extract represents 40 grams of fresh gland, the clinical results are not always predictable.

Then, when used in adequate dosage, the cost alone is often prohibitive. An adequate total daily dose rarely falls below 10 c.c., and such amounts of extract usually retail at about $5.00. A daily total dose of 20 c.c. not uncommonly is needed to preserve a normal condition. Even more than 20 c.c. is sometimes necessary as a daily maintenance dose. Such amounts at such prices often fix the hormone cost alone at $1,500 to $5,000 per year. Obviously such costs are beyond the reach of the average patient.

Finally, and least objectionable, is the inconvenience and pain incident to the intramuscular injections of 5 or 10 c.c. at one time, and that amount repeated once or twice in 24 hours. This objection may be circumvented in part by having the assistance of an attendant and by the addition of 0.5 c.c. of 1 per cent procaine.[7]

In order to overcome the disadvantages of cortical extracts, there has been a 10-year search for the "vital crystalline steroid." This quest has been motivated by the belief that such a product probably exists, and that when extracted or synthesized, a cheaper, purer, more potent, and more predictably effective product will come into clinical use. So far, no such perfect steroid has been isolated or fabricated in quantities adequate for

clinical use. But the search has been attended by a much better understanding of the different types of metabolic defects of the Addison syndrome, and in a measure, has determined just what specific steroid corrects each particular and specific defect of this deficiency disease of the suprarenal cortex.

Certainly the most obvious and measurable defects of suprarenal insufficiency are, first, a loss of normal control of pigment deposit in the skin; second, a loss of the normal regulation of the carbohydrate metabolism; and third, a loss of the normal power of retaining the blood electrolytes. The first is unimportant, its basic cause is unknown, and the specific correcting steroid is as yet undiscovered. However, the defect of carbohydrate regulation and that of maintaining normal electrolyte blood levels are exceedingly important defects, and each may be effectively controlled by a specific steroid compound.[8] Since control of the electrolyte levels in case of Addison's disease is attended by such desirable clinical results as subsidence of gastrointestinal irritability, restoration of feeling of well being, gain in weight and strength and in the normal vascular tension, and since this control of the electrolyte level is brought about quickly and effectively by and only by the steroid desoxycorticosterone (Loeb[9] and Kendall[8]), it has been chosen as the crystalline steroid compound of choice for use in replacement therapy. Although these desirable clinical results are attainable by the use of desoxycorticosterone alone, it in no way corrects the defect in carbohydrate regulation,[10] and consequently lacks the ability to prevent a single symptom stemming therefrom. Fortunately, the consequences of this defect are not usually as grave as are those of electrolyte control. In passing, we call attention to the recent conclusion of Thorn[6] that, since Reichstein is now able to synthesize steroids with an oxygen atom on the C_{11} position, it ought not be long before corticosterone (a weak sugar and electrolyte controlling hormone) and hydroxycorticosterone (a strong sugar controlling hormone) are brought into clinical use, much as synthetic desoxycorticosterone (a strong electrolyte controlling hormone) is now employed.

Desoxycorticosterone was synthesized by Reichstein and Steiger[11] in 1937, and the following year Reichstein extracted the identical hormone from cortical tissue. Only the synthetic product has become available for clinical use. Because of its rapid absorbability, it is marketed as an acetate ester, thus prolonging its period of activity. Delayed absorption is further enhanced by dissolving the steroid compound in an oil, such as sesame or some other inert substance. This type of preparation has been devised for intramuscular injections because the steroid compound is impotent when taken by mouth and only weakly potent when administered sublingually. Three products have been listed as acceptable by the Council on Pharmacy and Chemistry,[5] and are marketed under the trade names of percortin, doca and cortate. Each product contains exactly 5 milligrams of the steroid compound per 1 c.c. of oily solution and of course possesses equal potency. Unlike cortical extracts, they are absolutely interchangeable.

Percortin is also marketed in sterile pellets 125 milligrams in size. They are intended to be used as subcutaneous implants. The main reasons for preparing a product for this type of therapeutic procedure is to obviate the necessity of daily hypodermic injections. Hormones in oil require a strong needle of larger bore than is used for aqueous solutions. There is more difficulty in filling and emptying the syringe, and there is always some pain attending the process. Also, it is not yet proved that a daily injection of an inert substance having the bulk of 0.5 to 1.5 c.c. is wholly an indifferent matter. Besides, the cost may be reduced almost half by substituting implantation of pellets for hypodermic injections. Then, too, despite esterification and oily solutions the delivery of the hormone is not constant throughout the 24 hours between injections. Finally, implantations are required only about once a year, whereas the hypodermic injection is a daily chore for life.

Before implantation is considered, the doctor and patient should be reconciled to spend two or three months in an attempt to determine as accurately as possible the daily hormone requirement of that particular patient. The daily dosage of the steroid compound is accomplished much as is the insulin dosage in case of diabetes. In both cases, it is a sort of clinical titration, a backing and filling method, differing only in the type of criteria which have come to be recognized as end points indicating adequate dosage.

The following is a satisfactory procedure for determining the daily hormonal requirement. First, give the patient 3 to 6 grams of salt each day. We prefer 3 grams. This may be given in the form of 1 gram enteric sodium chloride with each meal. Some prefer giving the salt in a flavored aqueous solution.[7] The important thing is that a fixed and adequate amount of sodium chloride be given from day to day. Such a procedure will reduce the daily requirement of the hormone and will give a more elastic and adjustable program. Then begin by giving a daily subcutaneous injection of 1 c.c. of the oily solution (5 milligrams of the steroid compound). The patient should be carefully examined each day, the physician taking particular note of increase in weight, vascular tension and pitting edema of the shins. Should there occur a rapid increase in weight or pitting edema, the daily dose should be reduced by half, but the daily injections continued. By trial and error, the appropriate dose may thus be determined which will give to the patient a feeling of well being, and his weight, strength and vascular tension will approximate normal.

Exceedingly great care must be exercised in not pushing the dosage beyond the endpoint of safety. A casual or indifferent attitude toward the useful signs of increasing weight, edema and vascular tension may be fraught with the gravest consequences. Edema, hydremia, cardiac dilatation, dyspnea and unusual irritability are signs and symptoms that the safe endpoint has been passed. It must always be remembered that desoxycorticosterone is a powerful drug, and, when used without meticulous attention to these signs, is a dangerous drug.

Assuming that a satisfactory clinical endpoint has been attained by giving a daily injection of 1 c.c. (5 milligrams of the hormone) and no untoward signs or symptoms have appeared in eight weeks, the patient, we think, is then ready for pellet implantation.

It has been determined by animal experimentation and clinical use that one pellet of desoxycorticosterone acetate, weighing 125 milligrams, when implanted under the skin, gives off to the implanted individual approximately .5 milligram of the hormone in 24 hours. If the patient's daily dosage requirement has been determined to be 5 milligrams of the steroid compound, then it will require the implantation of 10 pellets to meet adequately his daily hormonal needs. In our limited experience, we have found this procedure of standardization, as well as the indicated pellet implantation, relatively safe. In uncomplicated cases of Addison's disease, it gives normal electrolyte levels in the blood and corrects the important signs and symptoms arising from the single Addisonian defect of electrolyte control. Theoretically, such implantation should be effective for approximately 250 days. Practically, they may effect adequate control for 10 to 15 months.

The technic of implantation as developed by Thorn and associates is as follows: "The infrascapular region in the mid-clavicular or posterior axillary line is a convenient site for the implantation of pellets. Observation of strict asepsis is absolutely essential. Under local anesthesia a transverse incision 2.5–5.0 cm. is made. The pellets are implanted in the subcutaneous tissues preferably at a distance of at least 1.5–2.0 cm. from the site of the incision. With blunt dissection a small 'pocket' may be prepared for each pellet, the implantation of the pellet being facilitated by inserting the pellet through a small nasal speculum. Employing this technic it is possible to insert as many as 10–15 pellets through a single incision, 2.5–5.0 cm. in length."

As a further precaution against infection, it is advised that the pellets be passed through ether just before implanting. Also, great care is urged in handling the friable tablets with metal forceps in order that they may escape a crushing grasp and thus preserve the calculated daily rate of pellet absorption. Also when "dropped" into the subcutaneous pockets, care should be exercised to plant them 1.5 to 2 centimeters away from the line of incision, thus guarding against pellet extrusion.

Other technics for the implanting of crystalline hormone pellets, not only for desoxycorticosterone acetate, but also for the estrogens [12] and testosterone propionate,[13] have been devised. Special attention should be called to the recently developed technic of De Maio [14] who suggests implantation by means of a small trocar and glass rod obturator. This reduces the length of the skin incision and so simplifies the implantation technic that it bids fair to become a simple office or at least dressing room procedure.

Although pellet implantation is a moderately satisfactory and perhaps the best method for treating uncomplicated Addison's disease at this time, it has no place in the treatment of crises of adrenal insufficiency, whatever the

cause. The common crises are those arising from neglect in treatment, the complications of intercurrent infections, surgery or accidents, overheating, or the administration of thyroid hormone. Adrenal crises may also occur in otherwise normal patients who have had bilateral adrenalectomy, or bilateral hemorrhage into the suprarenal cortex (Waterhouse-Friderichsen syndrome). These complications are still best treated by rest, intravenous sodium chloride solution, cortical adrenal extract, desoxycorticosterone acetate in oil,—all in quantities relatively massive as compared to the maintenance or standardizing doses previously recommended.

Also, it is obvious that pellet implantation is an inappropriate method for administering desoxycorticosterone acetate as a therapeutic test in borderline cases. However, when given in oil by daily hypodermic injections, the diagnostic use of the synthetic hormone is one of the cheapest and often most conclusive diagnostic procedures. Neurasthenics and chronically nervously exhausted patients are not impressively improved and do not show decisive weight gain. Addisonian patients do. Since 100 per cent diagnosis must always precede any thought of pellet implantation, it seems appropriate at this point to divert to a sort of thumbnail outline of diagnostic procedures:

1. Roentgen-ray of the suprarenal glands, when done by special and careful technic, will often reveal some degree of calcification in the suprarenal region. Since it may show marked calcification in patients showing only mild evidence of insufficiency, and none in many with gravest insufficiency, it can only be considered a presumptive test. Roentgenographic evidence of active or healed pulmonary tuberculosis has a similar value. Demonstration of a small heart is also of presumptive value.

2. Low fasting blood sugars and "flat" glucose tolerance curves are merely suggestive.

3. The Cutler-Wilder [15] test, the concentration of the chloride in the urine when a diet poor in sodium chloride and rich in potassium is given for 54 hours, is an excellent test to be used when other methods have failed in borderline cases, but it is too drastic to be used as a routine procedure.

4. The Kepler-Power water test [16] is a safe and useful routine test.

5. The reduction in output of 17-Ketosteroid excretion in the urine has a presumptive diagnostic value, but the determination of this steroid is beyond the average clinical laboratory.

6. Clinical response to the injections of desoxycorticosterone acetate is the last and most conclusive step in diagnosis. Taken in conjunction with the classic quartet of symptoms, this response justifies the beginning of the specific therapy as outlined above.

Another corollary to pellet implantation is the use of sodium chloride. As was previously pointed out, the need for cortical extract, oily synthetic hormone or pellet implants is reduced, and the treatment is more elastic and easily adjustable when the sodium chloride is given. Once again it may be

wise to caution that 3 to 6 grams of supplemental sodium chloride in 24 hours is desirable in all methods of treatment; but excessive doses either per os or intravenously is not advised. In at least two cases under our observation, disabling tendon contractures have occurred, and although the administration of excessive sodium chloride has not been proved to be the cause, competent critics have thought it possible.

The value of restriction of potassium in the diet has also been soundly advocated. Whereas this precaution is based upon the tendency of potassium to increase in adrenal insufficiency disease and fall with the injection of the crystalline hormone, it is questionable whether meticulous attention to its daily intake in the diet is justified. The daily weighing or measuring of foods, and the special cooking procedure that has been recommended are no small items of concern to a patient otherwise handicapped. Besides, when used in the presence of crystalline hormone therapy, there is a possibility of symptoms arising from low potassium in the blood. Perhaps a warning to patients to avoid foods known to be rich in potassium is adequate precaution in most cases.

Summary

1. Replacement therapy was forecast by the first clinicopathological reports of Thomas Addison.

2. Adrenal cortex extracts were the first effective replacement therapy for Addison's disease. They have their limitations.

3. Pure steroid hormones were isolated from the cortex, and desoxycorticosterone has been synthesized and, therefore, produced in such quantity at such cost that it has come into practical clinical use.

4. The use of desoxycorticosterone has led to a better understanding of the function of the suprarenal cortex and to the recognition of its limitation in correcting the defects occurring in Addison's disease. Despite this limitation, it is now the agent of choice in replacement therapy.

5. In uncomplicated cases it is best given by pellet implantation.

6. The procedure of choice for implantation is as follows:

a. Establish a diagnosis of adrenal cortex insufficiency.
b. Give from 3 to 6 grams of sodium chloride daily.
c. Advise against the use of foods rich in potassium.
d. If patient is not able to carry on in his usual occupation, begin daily injection of desoxycorticosterone acetate until the adequate daily dosage is determined. Continue the sodium chloride treatment.
e. Within two or three months, implant just enough pellets to meet the patient's calculated need. Continue the sodium chloride and only change the dose when the symptoms so indicate.
f. Redetermine the patient's daily hormone requirements and re-implant pellets about once a year.

g. Meet such symptoms as may eventuate from the recognized failure to correct the defect of regulating carbohydrate metabolism by appropriate dietary supervision and supplemental adrenal extract injections.

h. Meet the complication of crises by supplemental sodium chloride, adrenal extract and additional synthetic hormone.

i. Encourage the patient by assuring him that a better crystalline hormone compound is in the offing.

Illustrative Cases

Case 1. E. H., female, age 37, two years previously had begun to lose weight and strength. Bouts of vomiting occurred once or twice a month. The condition was regarded as an exhaustion syndrome. Pigmentation began one year previously. February 14, 1944, because of vomiting, exhaustion and loss of consciousness, she was hospitalized and treated for run down condition. May 6, 1944 she came to Colorado General Hospital having "awful black color," weakness and nausea. She was given NaCl, 1 gram t.i.d., plus 2 mg. desoxycorticosterone acetate. Blood pressure ranged from a mean of about 85 mm. Hg systolic and 60 mm. diastolic to about 100 mm. systolic and 65 mm. diastolic, and she gained 10 pounds in weight. There was no skin edema. She felt well. She thought that her skin was "much lighter." Optimal dosage of hormone had not been determined. She had slight fever after admission to the hospital, but roentgenograms did not demonstrate pulmonary tuberculosis. The Cutler-Wilder test, roentgenograms of the suprarenals, and therapeutic test were positive. She showed the classic signs and symptoms of Addison's disease. The dosage was to be further standardized and implantations made after about two months.

Case 2. J. C., male, age 16, in 1942 complained of exhaustion. The diagnosis was made by Dr. V. T. Austin of Urbana, Illinois, Addison's disease being suspected because a teleroentgenogram revealed a disproportionately small heart. Typical Addisonian crisis occurred with a blood pressure of 55 mm. Hg systolic and 45 mm. diastolic and blood urea of 48 mg. He was treated with intravenous salt and desoxycorticosterone acetate hypodermically. The patient developed anasarca. Dosage was reduced and he came to us in fair condition on 7.5 mg. every third day plus 4 grams of salt daily. During February and March of 1943 we determined his optimal hormonal daily dose to be 6 mg. plus 3 grams of salt. Therefore, 12 pellets were implanted on March 29, 1943. Subsequent rise of blood pressure to 150 mm. Hg systolic and 100 mm. diastolic called for salt withdrawal. After 15 months and without any other medication, his blood pressure was 110 mm. Hg systolic and 70 mm. diastolic and he was living a normal life.

Case 3. B. G., male, age 24, came to us January 9, 1940, with a diagnosis of Addison's disease. Dr. L. L. Hicks' clinical notes revealed the following. July 1, 1939 he suffered a heat prostration, with a blood pressure of 80 mm. Hg systolic and 70 mm. diastolic. He was relieved by salt and glucose intravenously. August 13, 1939 the blood pressure was 80 mm. Hg systolic and 60 mm. diastolic. He felt better after 5 c.c., 2½ c.c., and 2½ c.c. of Eschatin, and Addison's disease was diagnosed. November 10, 1939 a crisis occurred while he was out hunting. Blood pressure was 70 mm. Hg systolic and 60 mm. diastolic. He was rescued by glucose, salt, Eschatin 1 c.c. b.i.d., and 1 c.c. Percortin daily. Later he was placed on 2 c.c. Percortin daily and 5 c.c. Eschatin b.i.d. with much improvement. In January and February of 1941 the dose was further standardized, optimal dosage being 5 mg. plus 3 grams salt. On February 3 he was implanted with 10 pellets and given 3 grams of salt. Blood pressure remained within normal range, but edema appeared about

August 25, 1941, so salt was reduced, then discontinued. He carried on as a farm hand, but by December 24, 1942 he was reimplanted with eight pellets. He was about to return for third implantation.

Case 4. E. L., female, age 52, in 1935 began to feel tired and had spells of nausea. Her friends remarked that she was becoming brown and very dark by 1939. On October 10, 1939 Dr. Mathews of New Orleans diagnosed her condition as Addison's disease and referred her to Dr. Thorn of Johns Hopkins Hospital for treatment. The optimal dosage was determined and eight pellets were implanted June 22, 1940. In 1940 she was under our care during the summer. She was very pigmented, feeling fairly well, but with a systolic blood pressure of 180 mm. Hg. In the autumn Dr. Thorn had some of the pellets removed. February 15, 1942 she was reimplanted with four pellets. She returned to Colorado General Hospital in June 1943 and we implanted two pellets. August 24, 1943 blood pressure was 130 mm. Hg systolic and 90 mm. diastolic and she was feeling well.

Complication: Tendon contractions occurred in November 1940. Also, when she exercised she had hypoglycemic reactions which were controlled by a Seale Harris diet. She was able to work, save for tendon contractions.

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PERSPECTIVES OF PSYCHIATRY *

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PSYCHIATRY again stands on the world's doorstep, with the spotlight of the war setting it forth in high relief. Momentarily, as its representative before this group, I should be more literal, indicating that the needs for psychiatry are more acute, more pressing, more widespread than ever before. I am not too confident that psychiatry can rise with sufficient knowledge and strength and tact adequately to meet the challenge. I am confident that if these problems are to be met, if the wider recognition of their existence is to be grasped, the guidance must come through all organized medicine. If solutions are to be effective, it must be physicians—general practitioners, internists, surgeons—who further their development, who envision the many ramifications of psychiatry and who apply its principles and knowledge to these ramifications.

It is not merely a figure of speech to state that we are experiencing a world-wide psychosis. If we are to include in the concept of health, the mental status of an individual, never in the world's history have we had such an unhealthy state. Just as a widespread serious epidemic of a fatal disease commands the attention of all organized medicine, so should the present advanced mental disease of the world arrest all organized medicine. Furthermore, this state of affairs should not merely arrest our attention but should command our united attack upon the causes, the symptomatology, the treatment, and ultimately the prevention.

It was the brilliant Thomas W. Salmon who, as a result of his experience as Chief of Psychiatry of the American Army in the last war, drew an analogy between the emergence of psychiatry in the field of medicine at that time and Cinderella. Prior to the first World War, the practice of psychiatry had been pretty largely limited to the secluded cloisters on the periphery of the village, the State hospitals, known then as insane asylums. In those cloisters a relatively small number of hermit-like physicians had been gathering data in their study of human wrecks over a period of many years. Then came the first World War, and with it the need to understand and to treat the comparatively large number of casualties of a psychiatric nature that developed. Psychiatry became an extremely important branch of the Medical Department of the Army. Like Cinderella, it emerged from its hiding place because there was a pressing demand for it. Dr. Salmon described it as taking its rightful place among its sister specialties of Medicine and Surgery. In the present organization of the Medical Department of

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the Army, the Surgeon General has placed the Neuropsychiatry Division on an equal level with the Medical and Surgical Divisions.

We in this country know almost nothing of the suffering and the misery and the unhappiness, all of which are acute symptoms of mental ill health, that prevail in Poland, in Greece, in China, in the prison camps of Japan, in the concentration camps of Germany. Perhaps it is fortunate for our own mental health that we can, so inadequately, even speculate as to the vastness of this psychiatric problem. However, we have gone far enough in the participation of the war to recognize that just as in 1917 and 1918, a tremendous impetus will be given to psychiatry. The need for it is acute and extensive, and I am referring here not merely to the need for therapy, as important as that is. It is only one of the problems with major psychiatric implications in a nation at war, and in an Army waging that war. My comments are necessarily greatly colored and largely based on the orientation, a reorientation that I have experienced in the last 18 months in the Army, six of which have been spent in the Surgeon General's Office. As the individual responsible in some degree for the mental health of an Army of our size, and the psychiatric policies and practices which prevail in it, I quickly admit having a sense of great humility and a keen awareness of a vast responsibility.

It has been my intention to indicate that we are recognizing the importance of psychiatry as applied to the Army. Censorship prevents my indicating to you in any statistical way the size of this problem. You are familiar, however, with the approximate size of our Army. You are probably familiar with our screening method at the induction centers, in which the psychiatric rejections represent a considerable portion of the men eliminated. Of the men who are accepted, we must recognize that they have experienced from 17 to 36 years of a particular type of life in which they have done as they wished, migrated when and if they wished, worked at a job of their own choosing, and within the limits of our civil laws have lived at least 16 hours a day with free choice of their social, emotional and economic activities. The great majority developed a sense of security based on attachment to their home and family, to their job, and to their friends. And then, in a majority of instances through no choice of theirs, they were brought into the Army and as quickly were separated from these pillars of security and satisfaction that had always surrounded and supported them. In their stead they were regimented and disciplined and exposed to a strenuous existence, all of which are necessary elements to any Army. For many, soon the majority, these experiences are followed by more rigorous training, further separation, and then a departure for parts unknown, a step the psychological significance of which cannot be minimized. Then there is the period of waiting, probably more training, acclimation to new environments, often difficult climate and terrain, possibly with isolation and monotony. And finally, there is combat, the supreme test of adjustment.

One might summarize this whole picture psychiatrically by indicating that there are no experiences in the average civilian's life demanding such major psychological readjustments. There is no comparable series of events which places so much stress and strain on the adjustment capacity of every individual participating. The incidence of mental illness in civilian life is no small figure. We know that one out of every 22 persons will at some time or another be institutionalized because of mental illness, and this figure only represents the psychoses. We are familiar with the fact that at least 50 per cent of all patients who go to all physicians have functional disorders. We hear often quoted the fact that more than 50 per cent of all our hospital beds are for seriously ill mental patients, and such figures do not take into account the greatest number of personality maladjustments who never go to hospitals, often never go to doctors. They somehow manage to adjust their lives, carry their crosses, and either are not aware that they can seek help or are never under sufficient pressure to so do.

With these facts in mind regarding needs in our civilian population and then the picture of the stresses and strains in the Army, it is not surprising to discover or difficult to estimate the size of the psychiatric problem in the Army. Although our screening process at the induction centers eliminates a fair percentage of the large group of maladjusted individuals, even the casual visitor at a consultation service in a replacement training center, a regimental dispensary, is impressed with the opportunity, the need for psychiatry. Even more pressing, perhaps more surprising, is the experience of making rounds on the cardiovascular ward or the gastrointestinal ward or the orthopedic ward of an army hospital. Just as we find in civilian life, a fair percentage of the patients in these general medical and surgical wards are fundamentally maladjustment problems, with their emotions expressing themselves in their heart, their stomach, or their back. Many non-psychiatric critical observers have reported their keen awareness for the great need, not only of psychiatrists, but of a psychiatric understanding and foundation for every medical officer.

My title was "Perspectives of Psychiatry." The perspective of any picture depends on two fundamental factors: first, one's background of the subject matter; and second, his relative position in relation to the picture. Regarding the first point, the background of appreciation, reference was made above to the status of psychiatry prior to the last war, and its much wider recognition following that war. That psychiatry is still far too widely regarded as a highly specialized field concerning itself with an isolated group of patients, patients usually isolated from all other groups of sick people. Through the heroic efforts of some of our leaders, medical schools are teaching far more psychiatry than they did 20 years ago, but the fact remains that most of our students still leave medical school with no conception whatever of the anatomy of the personality or the physiology of the personality. The average physician in the study of his patient far too often makes no inclusion of the study of the individual's personality, even though

he may with meticulous care study the chemistry and physical pathology. One must conclude that even with the great advances of medicine and the equally great advances of psychiatry, the latter is still only vaguely appreciated in its universality and the applicability in general medicine. We must admit of the scotoma that in no field of medicine is there so much obvious observable and yet almost totally ignored pathology in every day life as is seen in the field embraced by psychiatry.

Further evidence is seen in the curious dichotomy which has separated psychiatry from public health. A few of our more progressive states have Mental Hygiene Commissions, but these are pretty largely concerned with the administration and the social legislation connected with the state psychiatric institutions. Rarely is psychiatry included in the field of preventive medicine, which is another admission of our failure to recognize the widespread prevalence of mental ill health and the comparatively simple measures which might be utilized in its prevention.

It has long been my contention that the blind spots involving this subject are in part the fault of psychiatry, and more particularly the psychiatrists themselves. Far too long have they been inclined to an isolationism. Too many times their presentation before non-psychiatric audiences have been too involved, too technical, sometimes verging on the mystical. The group as a whole has been guilty of withdrawing, and in many instances even losing contact with the progress of medicine in general. Fortunately, these failures of the past are being recognized, and I can assure you that many of us are making strenuous efforts toward their correction.

If we conceive psychiatry as the special field of medicine concerned with the thinking and the feeling and the behavior of a man, and particularly those deviations which make him ineffective or a threat to our social system of living, then we should recognize that the fundamental principles in this field should be a basic medical science and not confined to a specialty. And now the war, like a cloudburst, has fallen upon us, and malignant psychopathology is evident on all sides. The suffering and the pain, yes, and the mortality, will be greater than the combined effects of the 10 greatest epidemics that the world has ever known. Nor does one have to go to the psychopathy of Germany or to the tragedy of Greece, Poland, Belgium and Denmark. One sees the direct results of the stresses and strains within our own Armed Forces. One can see it in the firesides of our own civilian life.

All this leads to my second point regarding the perspective of a particular picture, namely the relative position in which one stands. In my own position, my subjective feeling is that I am standing in a valley, surrounded by mountains, mountains each of which presents challenges to be climbed. In fact, I feel they *must* be climbed, and climbed immediately. Each represents an opportunity, a necessity of a particular job that is included in my vista, and the acuteness of the situation and the pressure of time make immediate action imperative. May I describe some of these mountains, not only because of your interest in psychiatry and its application in the Army,

but because in almost every instance there are far reaching implications which apply to our civilian situation, both present and future.

The first mountain in my perspective of psychiatry as it is practiced in the Army is its intimate relationship to the other fields of medicine, particularly internal medicine and surgery. Much more so than in any civilian situation, our physicians in the military forces work in groups and with a closer liaison between the various specialties than prevails in the civilian hospitals or clinics. There are many factors which lead to this close working relationship. A soldier with any type of disability which prevents his full functioning in the field becomes a hospital patient. We do have dispensaries for very minor difficulties, but the soldier is subject to a rule of all duty or no duty. He is either entirely on the job or he is in the hospital; there is no intermediary for even temporary disposition. The result is that we see many more functional complaints than appear in the civilian hospital. An immediate result of this fact is a very free usage of a consultation system between all departments within the hospital. Perhaps the lack of competition between the medical confreres facilitates this system. No one need fear losing his patient to the consultant. The fact that there is no monetary factor is also a strong influence toward the frequent usage of consultations. Regardless of causes, the total result is a very close relationship between the internist, the surgeon and the psychiatrist. There is no doubt that this system makes it possible for the psychiatrist to maintain a much closer relationship to the general progress of medicine and surgery than he ordinarily does in civilian life. It is equally true that the internist and surgeon have a much closer contact with psychiatric problems and treatment than the civilian hospital permits. In many Army hospitals, all cases for elective surgery have a pre-operative psychiatric consultation. It is to be expected that all fields of medicine will benefit by this closer relationship, and it portends the possibility of a much wider utilization of psychiatry, and also the group practice method of medicine which encourages such.

A second mountain in my perspective of psychiatry, based on our experience in the Army, is the importance of the group welfare in contrast to the importance of the individual. The practice of medicine is pretty largely developed on the basis that the individual is the all important unit, and in our private practice of medicine, including psychiatry, our interest and concentration have been on the individual, his needs and his problems, his symptoms and his treatment.

In the Army, we have of necessity focused our attention, particularly in psychiatry, on the welfare of the group. Our management of a particular individual is many times entirely guided by our concern and interest in the group. In fact, I suspect that in some instances, those of us in the practice of psychiatry in the Army have had to alter certain of our principles which we believed in and practiced in civilian life.

Specifically, we have situations in which to some degree the attention to and consideration for the individual has to be sacrificed, perhaps more lit-

erally compromised. Thus we may find an individual who is fundamentally a neurotic person, who capitalizes with a considerable amount of conscious intent on his psychoneurotic ailment. In the Army he is sometimes called a "gold-brick." The fact that he constantly capitalizes on these symptoms makes him no less a neurotic, but this conscious exaggeration of his symptoms is recognized by his fellow soldiers, by his officers, and by medical officers. Sometimes they are unsympathetic with him and his behavior is a liability to the group morale. In civilian life we could spend time and effort in an attempt to change him, as well as to manipulate his environment in so far as it might be possible. In most instances, we can do neither effectively in the Army and often have to meet this problem by disciplinary measures. Another example is observed in the rather frequent experience of a type of individual who is assigned to overseas activities. He reaches the port of embarkation, but somehow or other manages to miss his train, to miss his boat. According to his story it is always an unhappy accident, but everyone else appreciates that it is a very fortuitous accident. Many such individuals merely need reassurance for their "gang plank jitters"; others are undoubtedly what we would term, in psychiatric parlance, neurotic characters. In the Army nomenclature, they are termed constitutional psychopaths. Our best management in the majority of such instances is the application of disciplinary measures and not psychiatric therapy. If we treated either of these types of problems with our civilian psychiatric methods (even if the manpower situation permitted) where the individual was paramount, the whole unit would suffer an acute drop in its morale and in its confidence in its officers, because even the most stupid individual can see the conscious purpose of the soldier in such behavior.

Furthermore in the Army, regardless of whether it is an antitank squad, whether it is an infantry platoon, whether it is a team in a B17, in all instances they are a team. They must work as a group, and their efficiency depends upon the coöperative efforts of every man in the group. As a consequence, throughout the Army the group becomes paramount and the individual, in some degree, losses his identity.

In the practice of medicine in the Army, we must follow this lead, and consider first the welfare of the group rather than that of the individual. This principle has certain implications in civilian medicine. It may be, at least in as far as psychiatry is concerned, that our great investment of interest and attention to individuals has tended to make us lose interest in the group. In the Army, chiefly because of our shortage of manpower, our psychiatric therapy is planned and administered on a group basis. Our psychotherapeutic sessions, the activities involving occupation, recreation, education, are almost entirely given on a group basis rather than on an individual basis. As a result we are learning many things about how we can manipulate a group, its attitude, its motivation, its behavior. We are learning various therapeutic influences which one member within the group may have upon other members of the group, and conversely the enforcement by

the group of opinions and attitudes on an individual member. In view of our acute shortage of psychiatrists in civilian life, the methods and results learned in the Army may greatly influence our civilian practice of psychiatry. This method is not new but its extensive use because of necessity and consequent improvement within the Army may be expected to provide some very valuable experience applicable to civilian practice and needs.

A third mountain of challenge from my present vantage point concerns our evaluation of personality. My immediate and practical concern is the development of the best methods possible to select those recruits whose personalities are most suitable to serve in the Army. In the neuropsychiatric examination in our induction centers we are greatly interested in how we can best accomplish this, so that from the large number of men who pass through these centers daily, we may pick those who are most likely to succeed. Never before have we had so rich an opportunity to study selection methods. Not only are we able to learn of our mistakes subsequently, but much more important, we are able to see how the man works out in the job given him.

From our meager data at hand we are aware, at least at the moment, of many paradoxes—paradoxes that indicate the inadequacy of our knowledge and methods. We know that many men whom we picked for the Armed Forces fail. We know that many whom we learn through closer scrutiny after their acceptance, have had a long history of maladjustment and yet make an unusually enviable record in the Army. Our job is an extremely difficult one. We must attempt to evaluate how an individual is going to withstand the stresses and strains that we know to exist in Army life, in a period which at most averages two or three minutes. Obviously this cannot be adequately accomplished, and yet that is our responsibility and we must accept it. As a result we have developed, and are in a continuous process of further developing, rapid selective methods which will aid us in determining a man's stability, a man's emotional maturity, a man's intellectual capacity, and a man's sense of social responsibility.

The implications from this experience in selection may have, in fact, should have, tremendous value for our civilian life. The most immediate illustration that I could cite is the psychiatric evaluation of our prospective medical students. Very possibly I am wrong, but I know of no medical school that makes any attempt to evaluate psychiatrically its incoming students. It is widely recognized that many of our failures in medical school are due entirely to personality difficulties. In the Army, we have become disconcertingly aware of the fact that an unreasonably large proportion of all Army officers retired because of psychiatric difficulties are medical officers.

This same experience and knowledge which we are gaining from our psychiatric evaluation of soldiers at Induction Centers can apply to many other problems, in addition to the examination of prospective medical students. It undoubtedly can be used effectively in many fields of industry, in

business, and in other professions. Many of the devices that we may be able to perfect, which will aid in the selection of men who can become a success in the field that they choose, will be of inestimable value to that field and the individuals concerned as well as even a greater saving to those who are excluded.

A fourth mountain to be climbed from my valley is the opportunity to study and evaluate the adjustment process under periods of great stress. As has been indicated above, there is probably no civilian situation which presents the necessity for such radical adjustment processes as are demanded within the Army. This applies not only to the immediate training situation when a recruit leaves the security of his home situation and enters the discipline and regimentation and strenuous existence of Army life. Very surely, there is nothing that is comparable to the adjustment necessary by the former civilian when placed in a wet, muddy fox-hole, exposed day after day to shell fire and constant threat to life, with inadequate sleep, nearly impossible physical conditions, and cold K rations day after day.

Many personalities can withstand this sort of thing for a time. We are convinced that a great majority of those who do break under such circumstances could not possibly have been weeded out by any psychiatric or psychological screening device that we now know. Nevertheless, even within that group, there is a differentiation of those who can stand stress for five or six days, others that can stand it for two or three weeks, others that can apparently withstand its strains indefinitely. There is no doubt that every individual is very grossly affected, is probably changed in certain fundamental portions of his personality. It is a rare opportunity to attempt to determine the significance of various factors in the individual's past life experience, his early psychological trauma and the influence in his childhood and adolescent up-bringing as they affect his adjustment capacity. It is to be regretted that, under terrific pressure of war and our shortage of manpower, we do not have research facilities to study such situations in detail. Obviously this is impossible, but I hope we can gather meager bits of information and observation together from many sources and observers to crystallize some findings that well might revolutionize our psychiatric methods, very possibly our psychiatric concepts of what is and is not important in the developmental influences of an individual's life.

With all this opportunity to study the soldiers who can and those who cannot withstand the stress, there is the corollary of an equally important opportunity for us to attempt to find aids and provide assistance to help them adjust. Thus we have become acutely conscious that motivation is an extremely important psychological factor in aiding the individual to achieve his goal. We have learned that if a man's aim, if his desire, if his wish is sufficiently strong, this motivation may influence his adjustment capacity more than any other factor. If the job seems important enough to the individual and if the individual feels that he is important enough to the accomplishment of the job, his adjustment capacities are tremendously

extended. We have also learned that when this motivation is weak, when a man does not have any clear conception as to why he is fighting or why he should be in the Army, our morale is low and our NP casualties are in direct proportion to the state of the morale.

Another equally important aid in this adjustment capacity is leadership. The principle is as old as the gregarious habits of man, and yet with renewed emphasis we again learn that where the leader takes a personal interest in his men, where he takes the pains to know them and their problems, to express his, and through him, the Army's appreciation of the men's efforts; when he establishes confidence in the men and receives their confidence, the adjustment capacity is again extended in an unlimited fashion. Equally, the converse is true, that where the leadership is weak, the morale is low and morale is synonymous with the mental health as reflected in the number of neuropsychiatric casualties that occur. This situation is clearly recognized as an analogy of the strong and good father contrasted to the weak and bad father in the primitive family constellation.

Still another mountainous challenge as seen from my vantage point is the opportunity to study the integration of the personality in its attempt to adjust to these many stresses and strains and its varied expressions of failure. More simply, the extent and variation in the psychopathology are unlimited.

To the internist and surgeon, perhaps most impressive is the number of individuals whose personality failure is expressed in somatic symptoms. The frequency with which an individual reflects his emotional disorder in the mirror of his soma, more specifically in his stomach or his heart or his cephalalgia or his low back pain, is sufficient to challenge the most organically oriented physician. There is no limitation, either in numbers or variety, to the study of these individuals. What are the factors that lead one man to express his emotional maladjustment in a dysfunction of his gastrointestinal tract and another man under the same stresses to utilize his cardiovascular system? Perhaps it is our system of medical education; perhaps it is our lack of orientation in psychiatry; whatever the cause, too many internists and surgeons are not stimulated to seek the cause or understanding of such human disease. In fact, their most common reaction is annoyance (unless the individual is a well paying client and then we are equally likely to be as unscientific). Rarely is this annoyance recognized for what it is, namely a defense for the physician's own ignorance.

The psychosomatic symptoms (and this is an unfortunate term in its implication that only certain physical complaints are psychologically influenced and thus fails to indicate that *all* symptoms are psychosomatic), however, are not the only opportunities which we may study to determine the early signs of personality dysfunction. Every medical officer in the Army is aware of the frequency of these signs and symptoms, both the psychological and somatic. Their relationship to the precipitating factors is, in many instances, much more obvious and more directly connected than in any comparable situation in civilian experience.

The recognition of these mountains that I have been discussing has come as the result of my good fortune of being in the Army and viewing them from that position. Having been until recently a civilian I also can see how much greater a rôle psychiatry must play in the problems of the civilian. I would like to indicate that this contribution to the country's health cannot possibly be made by the psychiatrists alone, but must be a much more important and integral part of the training and practice of every physician.

If mental health *is* the concern of medicine and if by mental health we mean happiness, efficiency, and social compatibility, then the principles of psychiatry must apply, not only to each of us as individuals, but to our social relationships to each other. The field must be recognized as inseparably linked to the social sciences and concerned with the adjustment and happiness of both individuals and groups. An emphasis must be placed equally on the preservation of mental health as well as the therapeusis of mental illness. We must include in our horizon the methods by which we can obtain a more happy and effective series of human relationships as they apply to family life, to marriage, to education, to economics, to politics, to sociology. We think, for instance, we want a democracy in which we can function as individuals and achieve the personal satisfaction and security of a full and healthy life for every person. We presumably fight for this liberty and freedom and equality, and yet within our own country harbor one of the greatest racial problems existing in the world today. We have paradoxes in our own practice of medicine. We must face the fact that, idealistic as we physicians think we are, we know the problem of medical care for the indigent is far from solved.

Perhaps you may feel that I am going far afield from my subject of the perspectives of psychiatry. You may ask what have marriage and economics and politics and interracial strife to do with psychiatry? You may say they are social problems. It is true they have nothing to do with blood chemistry or surgical technics, but they do vitally concern man's happiness and unhappiness, his motives and emotions. And these are his mental life and his mental health or ill health. They are directly related to medicine and must become a vital concern to medicine.

I do not mean to imply that psychiatry has the answer to any of those questions. I do not think it has, but I feel strongly that it should contribute an opinion, suggestions, a point of view. However, it must yet make great progress in its fund of knowledge and experience and its therapy. If this is ever to be accomplished it must be through its much wider understanding and utilization by every field of medicine.

In closing, may I return to some more immediate and concrete suggestions relative to the more limited field of psychiatry.

1. Medical Education. Every individual has his rationalized opinion about our medical education, and yet obviously from the ideas that I have presented, it might be concluded, and quite correctly so, that I feel strongly

that psychiatry should be a basic medical subject. This does not mean that there need not be specialists in the field. There must be. The universality, however, of emotions, of feelings, and their effect on the human body, makes it imperative that every individual practicing medicine be as firmly grounded in the field as he is in physical anatomy, physical physiology and physical pathology.

2. Public Health. An extension of this same principle should be made to preventive medicine, to public health. Again, if we accept the premise that mental health is a part of medicine, there can be only one logical answer to the necessity of including it in every preventive medicine program. Not only do I specifically refer to the prevention of serious and disabling mental illness, but much more important, the education and extension of our principles of mental hygiene, just as we educate individuals in physical hygiene. It is startling to recognize that there are more deaths from one expression of mental illness: namely, suicide, than there are from the five most communicable diseases. The paradox exists, however, that very few of our public health agencies concern themselves in the least with the mental health of the commonwealth.

3. Medical Assistants. As medicine becomes more of a social science and involves the assistance of research workers, of laymen assistants, of nurses, and for us in the Army our tremendously important medical administrative corps, we must recognize that these individuals should have a much closer contact in medicine from an earlier period in education than they do. In psychiatry, particularly, is this important, because no psychiatric team, whether it be in an out-patient clinic or in a hospital, can adequately function without the help of the clinical psychologist and the psychiatric social worker. It is to be hoped that some time our medical schools can become universities and include in their training these intimate associates and assistants of the physician.

4. Reorientation to the Importance of the Personality. In every medical course we start the student in devoting hours, weeks, months, in the dissection of the human body. We follow it with excellent courses in the physiology and the chemistry of this body. We are commendably grounded in the physical pathology of this body. Nonetheless, we suffer in our system of medical education by so much emphasis on the material, that the average medical student receives his diploma with only the vaguest conception that the most important part of his patient is the person who lives within the framework of the body. He leaves with slight, if any, idea that it is our ambitions and our strivings, our loves and our hates, our successes and our failures, our aggressivity and our passivity, that are probably the major determinants in the maintenance of health. From my viewpoint of psychiatry, medical education must reorganize to present an adequate orientation to these facts.

5. Convalescence. The recovery of every individual from every type of illness is very possibly determined more by his psychological life than any

other factor. Through some sort of curious scotoma, the consideration of this factor has been conspicuously absent in most studies of the process of getting well. Because it happens regularly, we assume that the operation will heal, the pneumonia will resolve, the decompensated heart will readjust. We have vaguely been aware of the fact that the recovery of a gastric ulcer does have a more direct and obvious relationship to the patient's emotional life. In general, we have ignored the emotional life in our general medical and surgical patients both before and after our specific treatment. For pragmatic reasons in some cases, psychiatric study before emergency medical or surgical treatment is not so important as after such treatment. Our lesson learned in the Army as to the importance of conscious motivation and our recognition of unconscious motivation make it obvious that such should be considered in every convalescence. The physician who fails to do so is an offender against his patient—as well as against the best practice of medicine.

6. Reorientation to Concepts of Mental Health. No field of medicine battles against such a welter of superstitions and misconceptions regarding its patients and methods as does psychiatry. Unfortunately, our greatest lack of understanding and most frequent source of misunderstanding lie in the medical profession itself. Again it may be in our system of medical education; it may be in the historical evolution of psychiatry from the period of werewolves and dungeons; it may be in the incomprehensible jargon of some psychiatrists; it may be in part the intangible nature of the subject in contrast to operative technic and stethoscopes or roentgen-rays; it may be the presumed necessity to defend our individual and naïve belief that each of us is a "normal" personality; whatever the causes, the fact remains that the physician's bungling of psychological factors keep thousands of cults thriving. Because he is a physician and thus the authoritative source of opinions for the layman, his attitude and understanding of psychiatry can and do color the public attitude. And even though progress has been made the public conception is still a blurred picture of disgrace and fear, mysticism and self-exemption. Is it too much to hope that the medical profession might take a more forceful initiative to gain enlightenment and disseminate it?

May I express my appreciation for your patience and your attention. I hope I may have conveyed clearly my own vistas of the psychiatric mountains to be climbed. My most important perspective tells me that they are *our* mountains—they face every organized group concerned with medicine and the changing order. Will we climb them?

CHOLELITHIASIS IN SICKLE CELL ANEMIA *

By H. Stephen Weens, M.D., *Atlanta, Georgia*

Introduction

Since the first description of sickle cell anemia by Herrick [1] a rather voluminous literature about this disease has accumulated. Though the various clinical and pathological features of this condition have been thoroughly studied, the occurrence of cholelithiasis in sickle cell anemia has received very little attention. Hein, McCalla and Thorne [2] described the case of a young adult negro with sickle cell anemia in whom, on autopsy, stones in a thickened gall-bladder were found. They were able to recognize a similar finding in two other cases recorded in the literature. Campbell,[3] discussing the abdominal symptoms of sickle cell anemia, believed that true biliary colic may occur in this disease, and Schaefer [4] described the presence of gall-stones in a patient with this condition. A review of the literature reveals that biliary calculi are not infrequently recorded in autopsy reports and case histories of sickle cell anemia, but the significance of this finding is usually not recognized. Commonly used textbooks of gall-bladder disease do not mention sickle cell anemia as an etiologic factor in the development of gall-stones in the colored race.

Cholelithiasis in sickle cell anemia appears interesting and important in view of the evaluation of the abdominal symptoms observed in this illness. The occurrence of gall-stones in this disease may also numerically influence the incidence of cholelithiasis in the negro about which there is much controversy.

For these reasons we thought it of interest to report the following cases of sickle cell anemia in which the diagnosis of cholelithiasis was made clinically and roentgenologically and to examine the incidence of cholelithiasis in sickle cell anemia on the basis of autopsy reports recorded in the literature.

Case Reports

Case 1. H. D. S., a 13 year old colored male, was first seen in the out-patient department in 1942 when the diagnosis of sickle cell anemia was made. There was a history of frequent episodes of abdominal pain since the age of four. The pain was localized in the epigastrium and in the left upper abdomen and radiated to the back. These attacks were frequently associated with soreness between the scapulae and over the sternum, and with aching in the knees and ankles. The family history disclosed that a younger brother was known to have sickle cell anemia.

Physical examination revealed icterus of the sclerae and pallor of the mucous membranes. The spleen was enlarged and quite firm. A systolic murmur was heard

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over the apex of the heart. Slight tenderness was elicited over the spine and sternum. There were several small scars noted at the anterior aspects of both legs.

Laboratory studies: Numerous red blood cell counts ranged from 2,690,000 to 4,350,000 with hemoglobin values of 9.0 to 10.6 gm. From 55 to 95 per cent sickling was observed within 24 hours. An icterus index was 19 and the serum bilirubin 2.0 mg. per cent.

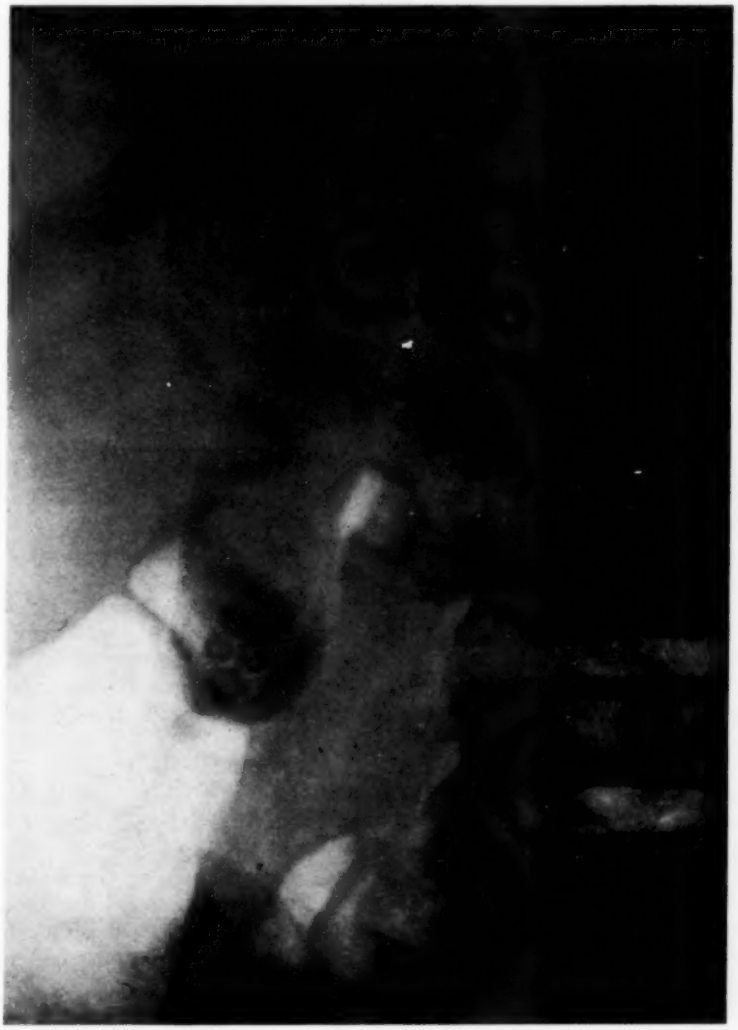

FIG. 1. *Case 1.* Colored male, age 13. Cholecystogram shows normal filling of the gall-bladder and 6 calculi.

Roentgenological examination: A film study of the abdomen revealed six facetted stones in the right upper abdomen. The dorsal and lumbar vertebrae showed a rather coarse trabeculation and were somewhat osteoporotic. The vertebral bodies appeared decreased in height and increased in width. The examination of the skull revealed that the bones of the calvarium were thickened owing to widening of the diploe which

had a granular, osteoporotic appearance. The inner and outer tables were thin, and no vertical striation was demonstrated. The gall-bladder filled well in subsequent cholecystograms. The stones were visualized within the gall-bladder shadow and were found to be freely movable. The calculi had a non-opaque center surrounded by several layers of calcium with perpendicular striation (figure 1).

Comment. In a 13 year old colored male with typical signs of sickle cell anemia, gall-stones were demonstrated. Roentgenologically, the calculi resembled mixed pigment stones. The gall-bladder apparently had normal function. Biliary calculi are unusual in a patient of this age and should draw our attention to the possibility of increased production of bilirubin as a result of a chronic hemolytic process.

Case 2. C. S., a 24 year old colored female, known to have sickle cell anemia, was admitted to Grady Hospital in January 1944 for treatment of a chronic leg ulcer. Since the age of 13 she had had frequent episodes of mild abdominal pain not associated with nausea and vomiting. The pain began in the umbilical region and radiated to the right upper abdominal quadrant and back. Fatty and greasy foods were well tolerated, but the ingestion of certain vegetables caused abdominal discomfort. The stools had normal color. For the past seven years the patient had suffered from a chronic ulcer on the right leg which had been treated intermittently with conservative methods and skin grafts. During the past four months she had suffered from two attacks of joint pain.

Slight icterus of the sclerae and pallor of the mucous membranes were noted. The lungs revealed no pathologic changes. A systolic murmur was heard over the precordium, but the heart was not enlarged. There were no significant abdominal findings. A sharply circumscribed ulcer, measuring 3 cm. in diameter and showing several bleeding points, was seen at the anterolateral aspect of the right lower leg. This ulcer revealed healthy granulation tissue, and its edges were not undermined. Scars were observed on the left lower leg.

The erythrocyte count was 2,560,000 with a hemoglobin content of 8 gm. A blood specimen from the fingertip, after compression of the finger with tourniquet for five minutes, showed about 80 per cent sickling. About 40 per cent sickling of the red blood cells was seen in the counting chamber. A small number of nucleated red blood cells was noted. The serum bilirubin was 6 mg. per cent. Numerous pus cells were present in the urine sediment. The Kahn reaction was negative.

A cholecystogram (figure 2) disclosed five facetted calculi, from 3 to 7 mm. in diameter, lying within the gall-bladder shadow.

Comment. A 24 year old patient with mild abdominal pain, chronic leg ulcers, and the blood findings of sickle cell anemia was found to have gall-bladder stones. Clinically, it seems to be difficult to rule out cholelithiasis as the cause of the vague abdominal symptoms.

Case 3. J. R., a 35 year old colored male, was admitted to Grady Hospital for study in November 1943. In 1929 he was found to have sickle cell anemia, and since that time he had been admitted at various intervals for treatment of leg ulcers and for blood transfusions. During these years the patient frequently had attacks of abdominal pain which were interpreted as "crises" of sickle cell anemia. The pain was localized around the umbilicus and radiated to the lower abdomen and legs, and to the left upper quadrant. This dull aching pain was occasionally associated with nausea, but was not related to meals. The color of the stools was normal.

The sclerae were icteric and the mucous membranes were pale. The heart was enlarged to the left and a harsh systolic murmur was heard over the apex. The liver and spleen were not palpated. Both legs showed scars of healed ulcers.

Since the first admission to the hospital the red blood count had ranged from 1,800,000 to 3,100,000 with hemoglobin values of from 6 to 8 gm. Sickle cell preparations revealed 20 per cent immediate sickling, 75 per cent sickling after 12

hours, and 85 per cent sickling after 24 hours. The serum bilirubin was 3.4 mg. per cent and the blood cholesterol was 151 mg. per cent.

Roentgenological examination: The bones of the calvarium were thickened and showed generalized osteoporosis without evidence of perpendicular striation. The heart revealed marked generalized enlargement with prominence of the pulmonary

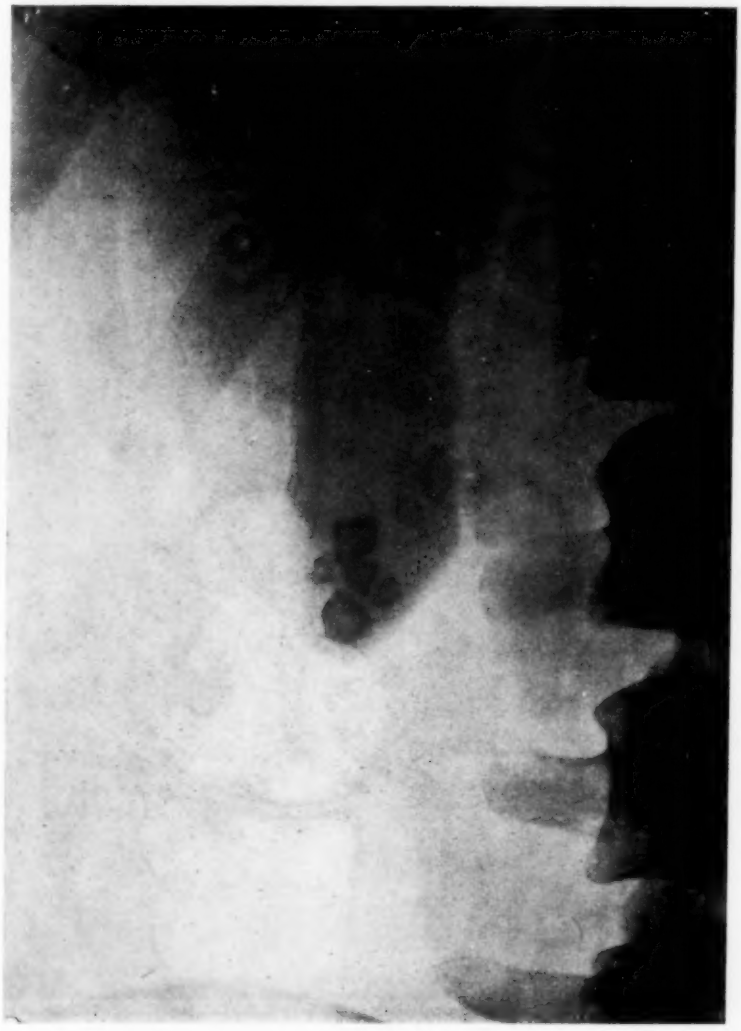

FIG. 2. *Case 2.* Colored female, aged 24. Cholecystogram shows 5 calculi and normal filling of the gall-bladder.

trunk. A cholecystogram in 1931 showed no gall-stones, and no filling of the gall-bladder was seen at that time. A film study of the gall-bladder area in 1943 disclosed numerous small facetted calculi which seemed to be localized in a contracted gall-bladder (figure 3). Fluoroscopic and radiographic examination of the gall-bladder after administration of contrast medium revealed faint filling. In the upright position the calculi descended into the fundus of the gall-bladder.

Comment. In a 35 year old colored male with typical symptoms and signs of sickle cell anemia, radio-opaque gall-bladder calculi were demonstrated. A cholecystogram at the age of 23 revealed no filling of the gall-bladder, suggesting that the function of the gall-bladder was impaired at that time. It may be possible to at-

FIG. 3. *Case 3.* Colored male, age 35. Numerous facetted calculi in contracted gall-bladder.

tribute some but certainly not all of the clinical symptoms of this patient to the presence of cholelithiasis.

Case 4. K. D., a 38 year old colored female, was admitted in January 1944 for the treatment of a chronic leg ulcer. Her past history and family history were noncontributory. She had been perfectly well until six months prior to admission when she injured her right leg. This trauma resulted in the development of a chronic

ulcer which became gradually larger and which had never healed. There was no history of episodes of abdominal pain or typhoid fever.

The mucous membranes were found to be pale, and the sclerae were not icteric. The examination of the heart, lungs, and abdomen did not reveal pathologic changes. An ulcerated area, about 5 cm. in diameter, appeared above the right ankle. The ulcer was sharply circumscribed and covered with small bleeding points. No varicose veins were seen. Several scars were noted on the left leg.

The erythrocyte count was 2,050,000 with a white blood count of 14,500 and a hemoglobin content of 6 gm. The tourniquet test revealed 30 to 40 per cent sickling of the red blood cells. The urine showed white blood cells in clumps and was otherwise not remarkable. The serum bilirubin was 0.4 mg. per cent.

Roentgenological examination: The Graham-Cole studies revealed faint filling of the gall-bladder which showed a smooth outline and normal size. Eight small facetted calculi were demonstrated in the fundus of the gall-bladder. After the fatty meal the gall-bladder revealed satisfactory emptying.

Comment. A 38 year old colored female with blood findings of sickle cell anemia developed a chronic leg ulcer after injury. Graham-Cole studies revealed the presence of small facetted calculi in a normal functioning gall-bladder. Remarkable is the absence of abdominal crises and other abdominal symptoms in this patient. Evidently we deal here with a case of silent cholelithiasis.

Discussion

Pathogenesis. Increased destruction of red blood cells is one of the characteristic features of sickle cell anemia. On disintegration of the red blood corpuscles, hemoglobin is liberated and converted into bilirubin. Hyperbilirubinemia in these patients is the result of increased blood destruction. This phenomenon is common to both sickle cell anemia and congenital hemolytic jaundice, in which latter condition Mayo [5] observed the presence of cholelithiasis in two-thirds of a group of patients.

According to Illingworth [6] it is believed that an excess of bilirubin in the bile will favor an aseptic precipitation of pigment in the biliary tracts. We have to assume that, once the nucleus of a gall-stone is formed, secondary factors such as stasis and infection will determine its ultimate chemical composition. In most case reports the calculi were described as multiple, small, greenish-black, soft pigment stones. The calculi in our patients were small, facetted and contained a peripheral layer of calcium.

Incidence of Cholelithiasis. The number of autopsy reports of sickle cell anemia, recorded in the literature, is comparatively small.[2, 3, 7a-y] Excluding those cases in which a very incomplete autopsy and clinical description is given or which are reported in the foreign literature not available to us, 44 necropsy reports were studied. In 12 of these cases gall-stones were found on autopsy or removed surgically during the course of the disease. The age and sex of these 44 patients are demonstrated in table 1. From these figures it will be seen that cholelithiasis was not encountered during the first decade. Gall-stones were, however, observed in patients who died during the second decade, and quite common in the third and fourth decades. There were no biliary calculi noted in patients of the age group above 40. Anemia

was not a characteristic feature of these latter cases, and it is very likely that they represented the so-called "sickle cell trait." Eight of these 12 patients in whom cholelithiasis was observed were males.

Since sickle cell anemia is a disease almost exclusively observed in the colored race, it may be interesting to compare these figures with statistics which deal with the incidence of gall-stones in the negro in general. There seems to be wide divergence of opinion about this subject. Mosher,[8] in 1901,

TABLE I

Total Number of Autopsy Cases					Number of Cases with Cholelithiasis			General Incidence of Cholelithiasis in the Negro (Jaffe)	
Age	Male	Female	Sex not given	Total	Male	Female	Total	Male	Female
0–10	6	6		12				0	0
11–20	2	6	1	9	1	1	2	0	0
21–30	8	5		13	4	1	5	0	3.28%
31–40	3	2		5	3	2	5	0.73%	7.5%
41–50	1	2		3				0	12.24%
51–60								1.86%	16.27%
61–70		1		1				4.34%	25.0%
Above 70		1		1				6.66%	20.0%
Total	20	23	1	44	8	4	12	1.04%	10.23%

reported an incidence of 5.5 per cent in the negro and 7.8 per cent in the white. These figures contrast sharply to reports by Bloch[9] and Alden[10] who were impressed by the rare occurrence of gall-stones in the Southern negro. Jaffe,[11] whose figures are in accord with most North American statistics, could demonstrate in a large series of autopsies that there exists a considerable difference in the incidence of cholelithiasis in the colored and white race. In white males gall-stones were found six times as often as in colored males, and in white females 1.7 times as often as in colored females. This author considered his autopsy material uniform and concluded that the difference could not be explained on the basis of diet, occupation or mode of living.

Jaffe's findings, recording the incidence of cholelithiasis in the colored race, are included in table 1 for comparison. From these figures it may be seen that cholelithiasis in the younger age groups is infrequent. In these age groups, however, gall-stones are most commonly encountered in sickle cell anemia. With the generally lower incidence of gall-stones in the colored race, sickle cell anemia may be a more important etiologic factor in the development of biliary calculi in the negro than is generally appreciated.

Cholelithiasis and Abdominal Crises. Episodes of acute abdominal pain, usually localized in the epigastrium, occur frequently in sickle cell anemia. Fever, abdominal tenderness, and leukocytosis during these crises may make it extremely difficult to differentiate such an attack from an acute

abdominal condition. Actually, as the literature reveals, a good number of patients with sickle cell anemia have been operated on for appendicitis, cholecystitis, and ruptured peptic ulcer.

As yet the cause of pain in the abdominal crises has not been satisfactorily explained. Hepatic infarcts,[12] splenic hemorrhages,[13] and nerve root pains due to vertebral changes [14] have been suggested. The occurrence of gall-stones in these patients will, therefore, immediately raise the question as to whether such crises could be explained on the basis of biliary colic. This seems unlikely, in view of the fact that many patients with sickle cell anemia do not develop cholelithiasis. It is also known that patients with sickle cell anemia and cholelithiasis have continued to suffer from abdominal crises after cholecystectomy. On the other hand it is entirely possible that many attacks of acute abdominal pain are not caused by crises but may be attributed to true biliary colic.

Summary and Conclusions

Cholelithiasis is not infrequently observed in patients with sickle cell anemia. Four cases of sickle cell anemia are reported in which gall-stones were demonstrated roentgenologically. A review of the literature reveals cholelithiasis in 12 out of 44 autopsy cases of sickle cell anemia on record. All 12 patients were in the age groups below 40 in which according to statistics cholelithiasis is not frequent.

The occurrence of biliary calculi in the negro is not rare. There is, however, sufficient statistical evidence to indicate that cholelithiasis is less frequently encountered in the colored race than in the white race. Since there is a lower incidence of cholelithiasis in the negro, sickle cell anemia gains relative importance as an etiologic factor in the development of gall-stones in the colored race.

It is not believed that the crises of sickle cell anemia can be explained solely on the basis of biliary colic. However, it seems possible that abdominal symptoms in some of these patients are due to cholelithiasis and associated gall-bladder disease.

The recognition of sickle cell anemia as a cause of acute and chronic abdominal symptoms is important in order to avoid unnecessary operations. The mere presence of biliary calculi in a patient with sickle cell anemia requires careful evaluation of all clinical symptoms before operation is advised, since it is commonly known that this disease increases the risk of surgical procedures.

Therefore, cholelithiasis in the negro, especially in the young negro, always demands search for the presence of sickle cell anemia.

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STUDIES ON THE PATHOPHYSIOLOGY OF SICKLE CELL DISEASE*

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The subject of sickle cell disease has been rather extensively studied with respect to its clinical [1, 2, 3] and pathological [4, 5, 6] aspects. Some work [7, 8, 9] has been done to study the disease in a dynamic physiologic way, especially with reference to the hemolytic mechanisms and the peculiar pathophysiology of the red blood cells so characteristic of this disease. Inferences are drawn from these studies to explain the terminal histology as well as many of the clinical aspects. Our interest has been centered on fairly long term studies of the pigment metabolism as one of the dynamic mechanisms which might lead to a better understanding of some phases of the disease process. The question of relative severity of the disease from patient to patient is easily confused by the protean manifestations of a disease such as this because of incidental involvement of more or less vital organs or tissues. For that reason we have chosen to study patients presenting the common hemolytic syndrome in varying degrees of severity.

Case Reports

Case 1. B. T., colored female, age 13 years, was admitted to the hospital complaining of pain and swelling of the ankles, elbows, fingers, and a sore throat. There was a history of growing pains beginning three years previously, and lasting for two years. The pains in the joints began six months before admission and occurred in intermittent attacks lasting several days. For the last month she had been in bed continuously. There had been some dyspnea on exertion in the preceding six months.

The eyes were known to have been yellow since early childhood.

The temperature was 99.4° F., pulse 118, blood pressure 98 mm. Hg systolic and 70 mm. diastolic, weight 67 pounds. She was asthenic in build, 5 feet tall, and moderately undernourished. The sclerae were slightly icteric. The tonsils were large, and the arteries of the neck pulsated visibly. The heart was enlarged to 9.5 cm. in the left fifth interspace. The rhythm was regular, the apex thrust forceful. There was a soft systolic murmur at the apex and along the left border of the sternum. The first heart sound was not accentuated. The liver and spleen were not palpable. There were swelling and tenderness with limitation of motion of the fingers, elbows, and ankles. Several small nontender nodules were felt on the posterior aspect of the left elbow.

The red blood cell count was 2.01 million, hemoglobin 7 gm., white blood cells 11,900, with 54 per cent neutrophiles, 37 per cent lymphocytes, 6 per cent eosinophiles, and 4 per cent monocytes. There was 75 per cent sickling of the red blood cells in a wet preparation in 24 hours. The urine was negative for urobilin and urobilinogen.

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The electrocardiogram showed a PR interval of .12 sec., QRS .08 sec., a rate of 104, and no significant changes from the normal curve.

Roentgenographic examination showed the transverse diameter of the heart to be 12.8 cm. and that of the chest 23.7 cm., with a prominent pulmonary conus. Roentgenograms of the bones and joints showed a general decalcification, periarticular swelling and effusion into the joints. There was some thickening of the inner table of the skull.

The course in the hospital was marked by a migration and slow subsidence of the joint swelling and pains uninfluenced by salicylate therapy, and a variable degree of low grade fever. A single transfusion of 300 c.c. of whole blood increased the blood count to 2.32 million per cubic millimeter. It continued to rise to a level of 2.7 to 2.8 million where it remained for the duration of the study.

Our studies were begun one month after admission, and revealed a rather constant degree of anemia, a leukocyte count of 10 to 12 thousand, and a constantly elevated bilirubinemia. The urinary excretion of urobilin never exceeded 3.6 mg. per day. The stercobilin excretion, however, showed an interesting cyclic variation over the two months' period of study (figure 1).

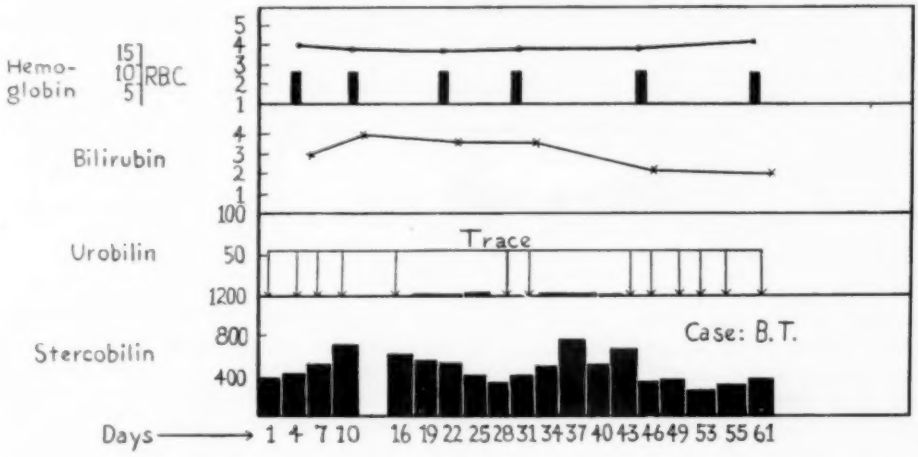

FIG. 1.

This case is a good example of the moderate degree of anemia associated with signs and symptoms very suggestive of rheumatic fever and carditis. Klinefelter [10] has reviewed the literature and reported 12 cases of his own of this picture of sickle cell disease simulating rheumatic fever. Only detailed study of them suggests that they are not rheumatic in origin, a conclusion not infrequently proved at autopsy.

Case 2. J. McC., a colored male, 13 years of age, was admitted complaining of migratory bone and joint pains of one week's duration. He had developed a toothache in a lower molar a week before the onset of the bone and joint pains. An abscess developed and ruptured through the gum. There were no gastrointestinal or cardiovascular symptoms. He had had frequent sweating since the onset of the present illness. The past and family history were irrelevant.

He was somewhat undernourished, was 4 feet 8 inches tall, and weighed 69 pounds. Temperature was 100.4° F., pulse 90, and blood pressure 90 mm. Hg systolic and 70 mm. diastolic. There was a definite icterus of the sclerae, and swelling and tenderness over the left mandible. The tonsils were enlarged and the anterior cervical nodes and submaxillary nodes were moderately enlarged. The heart was

slightly enlarged, both clinically and on roentgenographic examination. The apex thrust was forceful and there were loud harsh systolic murmurs at all valve areas. The liver was enlarged 4 cm. below the costal margin in the midclavicular line. It was not tender. The spleen could not be felt by any maneuver. The extremities were negative.

The red blood cell count was 3.0 million and the hemoglobin 8.5 gm. The white blood cells numbered 21,000, neutrophiles 87 per cent, lymphocytes 12 per cent, and monocytes 1 per cent. A wet preparation of the blood showed 75 to 80 per cent sickling in 24 hours. The urine showed 2 plus albumin, but was otherwise negative. The blood bilirubin was 5.0 mg., and the qualitative reaction was positive direct.

The icterus of the sclerae disappeared rapidly. The temperature varied between 99.2° and 100.6° F. daily for a week and then subsided to normal.

Our studies were begun on the eleventh hospital day and continued for one month (figure 2). The blood picture at that time showed red blood cells 3.3 million,

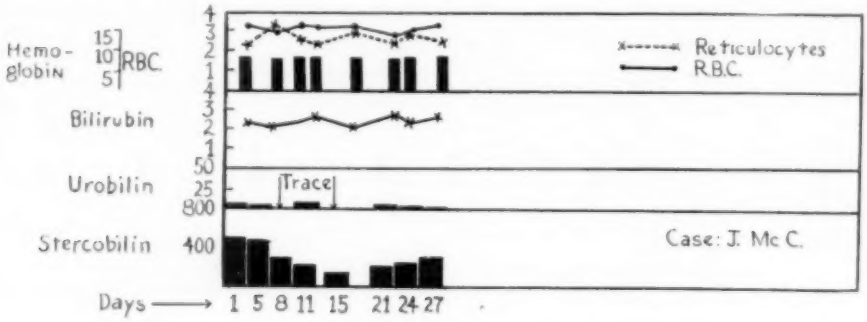

FIG. 2.

hemoglobin 8.8 gm., white blood cells 17,000, reticulocytes 11.6 per cent, and the blood bilirubin 1.8 mg. per cent, with a negative direct qualitative reaction. The intravenous hippuric acid test was normal (.74 gm.). A punch biopsy of the liver revealed some moderate hemosiderin deposits in the liver cells, slight fatty change, and moderate amounts of glycogen. No erythrophagocytosis was seen.

As can be seen from figure 2, there was little variation in the blood picture or bilirubinemia. The urobilin excretion varied from traces to 6 mg. per day. There was a very definite suggestion of a cyclic variation in the stercobilin excretion, as had been observed in case 1. It is obvious that if pigment studies were done at the nadir of the cycle one might consider that hemolysis, as evidenced by stercobilin excretion, was absent. There is further evidence in these two cases that the urobilin is not increased in these milder phases of hemolytic anemia.

The liver gradually receded in size, but was still palpable when he was discharged. Six months after discharge he was seen again. He had been in good health. The liver was not palpable, nor was the spleen. The sclerae were just slightly icteric.

The etiology of the hepatomegaly in this relatively mild case of sickle cell disease is not obvious. In the light of later studies we feel that it developed as a result of active sickle cell disease plus the effects of a suppurative infection, either one of which alone would probably have been ineffective.

Case 3. M. G. (the patient mentioned by Bauer [2]), a colored female, 19 years of age, when first studied had a long history of recurrent leg ulcers beginning when she was about 13 years of age, at which time she had had an ulcer of the left anterior lower leg which took five to six months to heal. When seen again in 1937 she had an ulcer of four months' duration behind the internal malleolus on the left ankle.

From that time on she had repeated recurrences of the ulceration in this site, and her red blood cell count had varied from a low of 750,000 to 4.42 million, usually running between 2.0 and 2.4 million. A week before the present admission she had noticed a sticking sensation in the left leg in the scar of the ulcer which had been completely healed for five months. It had not been traumatized. The scar broke down and formed a semilunar ulcer.

The patient was a well developed slender colored female. The temperature was 101° F., pulse 88 per minute, blood pressure 120 mm. Hg systolic and 78 mm. diastolic. The sclerae were lemon yellow in color. The mucous membranes were pale. The

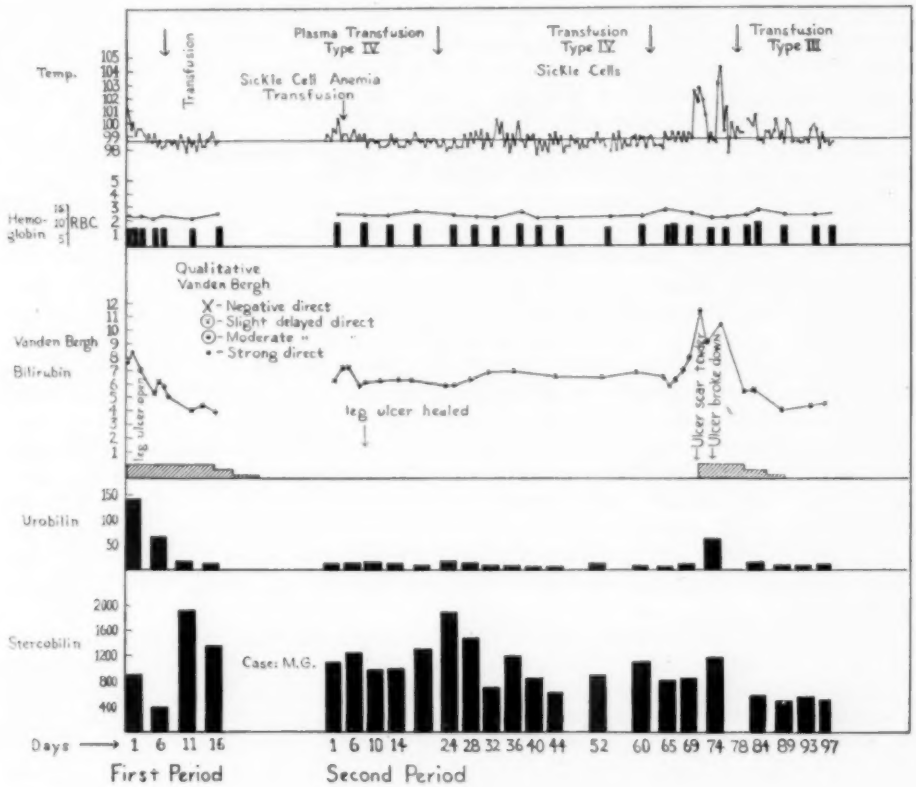

FIG. 3.

heart was not definitely enlarged clinically. The apex thrust was forceful. The liver was palpable and tender 3 cm. below the costal margin in the midclavicular line. The spleen was not palpable by any maneuver. There was an ulcer on the left ankle behind the internal malleolus 1.5 by .75 inches, shallow and indurated, and the skin was hyperpigmented about it. It was tender about the margins.

Electrocardiogram showed a PR interval of .14 sec., QRS .09. The T-waves were low in the first lead. Roentgenographic examination of the long bones and skull showed no changes.

The data from our studies (figure 3) were obtained beginning four days after the patient's admission while the temperature was subsiding. The red blood cell count was 2.4 million, hemoglobin 8.0 gm., white blood cells 9,000, neutrophiles 76 per cent,

lymphocytes 16 per cent, monocytes 6 per cent, eosinophiles 2 per cent. A wet preparation showed 100 per cent sickling in 24 hours. The blood bilirubin level was 7.2 to 8.0 mg. per cent with a positive direct qualitative reaction. This rapidly decreased to 3.6 to 4.0 mg. per cent with a negative direct reaction. The urobilin excretion was excessively high beginning at 135 mg. per day and rapidly decreasing to 10 mg. per day when the study terminated. The stercobilin excretion followed a very irregular course, possibly influenced by a transfusion of sickle cell blood which was given at the low point of the stercobilin excretion.

The leg ulcer healed nicely in about three weeks' time.

She was readmitted one month later for check-up and was asymptomatic. The leg ulcer was still healed. The red blood cell count was 2.45 million, hemoglobin 8.0 gm., the blood bilirubin 4.8 mg. per cent negative direct. She was given 500 c.c. of whole blood and the red blood cell count rose to 2.72 million, hemoglobin 9.0 gm. During this period, not shown in figure 3, the urobilin excretion varied from 8 to 12 mg. and the stercobilin from 500 to 1,300 mg. per day.

Second period of study: Two months later she was readmitted with the history that three weeks previously the scar on the left ankle had again broken down to form an ulcer. The red blood cell count was 2.36 million, hemoglobin 8.0 gm., and the white blood cells numbered 15,500. When we first saw the patient on this admission the leg ulcer was practically healed and she was asymptomatic. We continued our studies (figure 3) to observe the effects of transfusions of whole blood and plasma from active and inactive sickle cell disease. We were unable to be certain that any effect was obtained on the hemolytic process.

One week following a transfusion with 275 c.c. packed red cells suspended in saline from an inactive sicklemia patient, our patient developed a headache and began to run some fever. The ulcer scar became tender and broke down to form an ulcer. The temperature subsided and then rose again to 104° F. She lost her appetite, had some nausea and vomiting, some crampy abdominal pains, and a few loose bowel movements. The sclerae rapidly became deeply icteric, and the liver became tender and enlarged to 3 to 4 cm. below the costal margin. These symptoms and signs subsided with relative rapidity over a period of about five days. The leg ulcer then began to heal, and closed over in about two and a half weeks from the initial breakdown.

Besides the febrile clinical course with symptoms and signs of liver involvement during these two episodes, there was a sharp increase of urobilin excretion at the height of the symptoms and signs, the bilirubinemia increased sharply, and the qualitative reaction changed from negative direct through delayed to immediately positive direct reaction. This also subsided rapidly and the qualitative reaction reversed again. Since these studies, we have observed this same sequence of events during two other subsequent periods in this patient.

Case 4. P. T., a colored male, 16 years of age, was first seen in Charity Hospital in January 1939, at which time he was found to have a liver extending to the umbilicus. The spleen was not palpable. He had open leg ulcers bilaterally which had recurred intermittently over the previous seven years. Nine days before this admission his aunt had noticed that his eyes were getting very yellow. On admission the icterus index was 30 units, the red blood cell count was 2.2 million, white blood cells numbered 16,700. The urine showed albumin one plus. He was febrile for a period of eight days with a temperature ranging from 100 to 101° F. The liver receded to normal size before his discharge six weeks later. The leg ulcer persisted.

On his next admission in November 1939 he complained of abdominal pain. The sclerae were yellow, and the liver was palpable and tender 4 cm. below the costal margin. The spleen was not felt. The leg ulcer was still present. His temperature was 100.8° F. on admission, and remained elevated for four days. The red

blood cell count was 2.3 million, white blood cells 24,500, neutrophiles 88 per cent, lymphocytes 12 per cent, hemoglobin 5.5 gm. There were 3 to 4 nucleated red blood cells per 100 white blood cells. The icterus index was 50 units. He received three 500 c.c. transfusions. The red blood cell count rose to 2.89 million with 7 gm. hemoglobin.

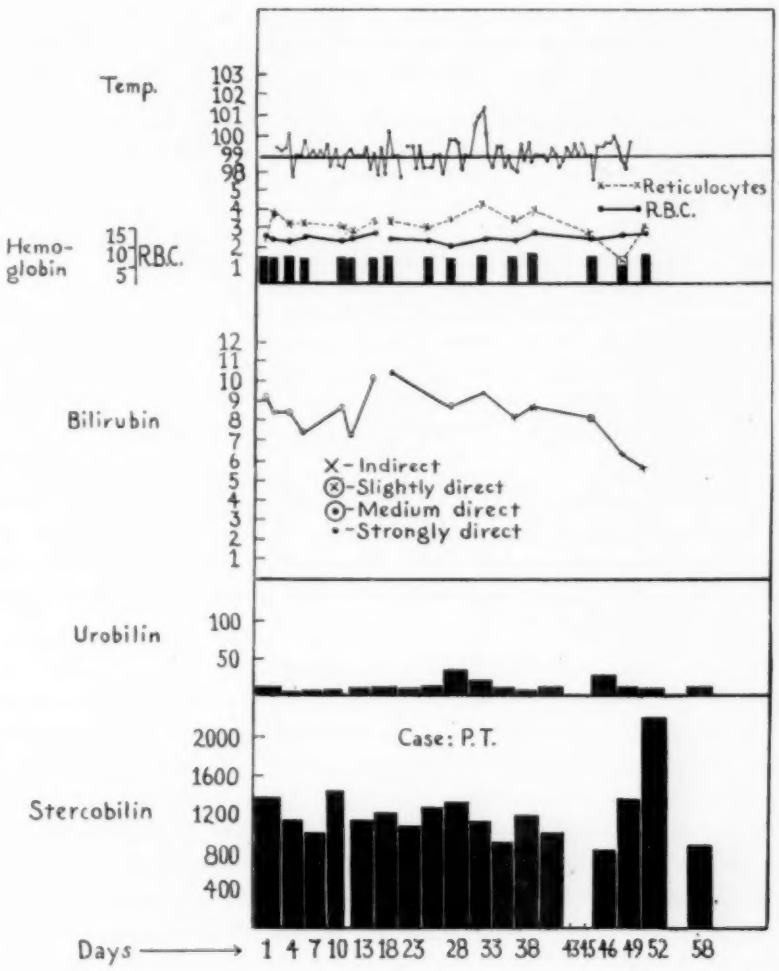

FIG. 4.

A month later he was admitted with the complaint of pains in his stomach. These pains were continuous, not related to eating, but were associated with anorexia and nausea, and severe headaches. There was no constipation or diarrhea. He had noticed his eyes getting yellow just a week prior to this admission.

He was a thin colored boy, temperature 104° F., blood pressure 108 mm. Hg systolic and 65 mm. diastolic, pulse 65. The sclerae were deeply jaundiced. The mucous membranes were quite pale. The axillary, cervical, and inguinal nodes were all enlarged. The lungs were clear. The heart was moderately enlarged to the left. The apex impulse was diffuse and forceful. There were no shocks or

thrills. There was a soft systolic murmur heard at all valve areas, but heard loudest in the third left interspace near the sternum. The liver was markedly enlarged, extending almost to the umbilicus. It was quite tender. The spleen could not be felt. There were scars and an open ulcer on each leg. Both ulcers measured 3 by 4 cm. in diameter.

The red blood cell count was 2.0 million, hemoglobin 5.0 gm., white blood cell count was 35,500, neutrophiles 80 per cent, lymphocytes 16 per cent, monocytes 4 per cent, with 4 to 5 nucleated red blood cells per 100 white blood cells. The urine showed one plus albumin. The icterus index was 125 units, and it decreased in two days to 50 units.

The temperature declined to normal over a nine day period, during which time he received 900 c.c. whole blood. It then remained at normal levels with frequent rises to 99.3 to 100.3° F.

A month after his last admission our studies (figure 4) were begun, at which time his liver was still enlarged and tender. The red blood cell count was 2.3 million, hemoglobin 7 gm., white blood cells 29,100, reticulocytes 14 per cent. The bilirubinemia was 7.4 mg. per cent, with a negative direct reaction.

The data from these observations, together with the clinical picture, suggest that this patient has a more active form of the disease which has been interrupted by periods of increased activity, which though not limited to involvement of the liver, nonetheless shows the phenomena observed in case 3 and case 2. In case 2 and case 4 we probably missed the early phenomenon of excessive urobilinuria, as this is evidently rather transient. There remains the clinical liver enlargement, the elevated bilirubinemia and the direct qualitative reaction of the serum bilirubin. We feel that although there was not the excessive urobilinuria as seen in case 3, the rises to 25 to 26 mg. per day in this case during the course of the hepatomegaly is suggestive evidence of functional disturbance of the liver. The tendency to cyclic alterations in the stercobilin excretion is not so evident in this patient, but more so in the urobilinuria than heretofore noted.

Discussion

We have been particularly interested in the apparent involvement of the liver in certain exacerbations of this disease. When we first observed it during these studies we felt that it could easily be explained by the stagnation and sickling of the red blood cells in the liver sinusoids as observed by Diggs [3] in the spleen and by Diggs and Ching [4] in the liver. Soon after case 3 of this group was studied, we observed the same phenomenon in a case of congenital hemolytic icterus [11] wherein the tendency to stagnation because of the stasis and the aggravated deformity of the red blood cells would not so clearly apply. This conception may, nevertheless, be pertinent in sickle cell disease, aggravating the anoxemia present in tissues, such as the liver, of those patients with the more severe anemias. Another point in favor of this idea is the marked transience of the phenomenon as is evident in case 3, the more or less frequent repetition of it, and its correlation with other evidences of exacerbations of the disease process such as the activation of healed ulcerations, fever, and leukocytosis, in the absence of demonstrable infections.

This picture of acute transient hepatomegaly associated with abdominal pains, nausea, anorexia, fever, headaches, leukocytosis, and hepatogenous

jaundice, may be designated as one type of abdominal crisis which occurs in this disease as it does in congenital hemolytic anemia.

It is thus far impossible to estimate the severity of the disease process on the basis of one factor alone. It is evident that the severity of a given case may vary from time to time, that in this disease as in others there are exacerbations and remissions, and that the gravity of the condition depends not only on the overall activity of the disease, but also upon what particular organ or system may be involved. Therefore, Bauer's suggestion [2] that the disease process be designated sickle cell disease has merit.

We have reported these four cases as representing various degrees of severity of a single syndrome as judged by the general health of the patients, tendency to exacerbations, degree of anemia, duration of the exacerbations, and the tendency of the leg ulcers to recur and to heal. It would appear that this particular type of crisis is more likely to occur and be more severe in the patients with evidences of the more marked degrees of activity.

The relationship of this transient hepatomegaly to the hepatomegaly observed by the pathologist is interesting to speculate on. Stasney [6] has studied the liver and spleen relationship in this disease, and described anew the marked congestion of the sinusoids and venous sinuses which seem to be the outstanding factors from a quantitative aspect. Hyperplasia and erythrophagocytosis by the Kupffer cells as well as the edema and degenerative changes of the parenchymal cells would add further to the increase in weight.

We feel that the degree of activity of the disease process is the most important factor in determining the gross and histological end results as viewed by the pathologist. On this basis Stasney's data suggest that those cases of lesser degrees of activity live longer (average age of his group I, 33.6 years) and have less pathological change (liver : spleen ratios near normal) and frequently die of secondary causes. His group II cases all showed more marked pathological changes. The average age at death of this group was 19 years. As Diggs has suggested, there is only a general correlation between spleen size and age groups, and there are notable exceptions in individual cases. It is probable that the explanation of these exceptions is to be found in the degree of activity of the pathophysiologic processes which produce the progressive histologic changes. Such processes of great intensity acting over a short period of time could cause histologic changes of the same degree as the same processes, only of lesser intensity, acting over a longer interval. Death, because of the disease or incidental complications, would interrupt the sequence at any point, thus causing apparent inconsistencies in the autopsy material.

It is this factor, the variable dynamic intensity of the disease, which is best illustrated by the clinical and laboratory material we have presented. At times it is difficult to recognize the cause and effect relationships of anatomic and physiologic changes. However, it is generally agreed that it is the genetically conditioned cellular physiologic aberration which is primary

in sickle cell disease. How this primary physiologic fault acts to produce such evident structural defects as the abnormal red cells and the vascular and thrombotic phenomena which lead to the histologic abnormalities we do not know.

Summary

Four cases of sickle cell disease with the hemolytic syndrome of variable degrees of severity have been presented in an attempt to illustrate acute transient hepatomegaly and liver dysfunction as occurring in certain of the abdominal crises of the illness. We feel that this tendency to acute exacerbations of the disease is generally correlated with the degree of activity of the disease.

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THE TREATMENT OF OBESITY BY APPETITE CONTROL: THE USE OF AUTONOMIC SUBSTANCES AND THEIR SYNERGISTS *

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The most common and important type of obesity is without doubt due to the overindulgence of food. The purpose of this paper is to discuss methods of influencing the diet in this form of obesity. There are, however, two other types although rare, that should be mentioned. Because of the prevailing confusion that these types are common they will be gone into in some detail, but it must be stressed again that they are relatively rare.

Unusual Forms of Obesity. These rarer forms of obesity are due to glandular disturbances and lesions of the central nervous system, especially of the hypothalamus. Their relative rarity has been stressed by many recent authors, especially Greenhill.[1] One usually diagnoses endocrine obesity when there is excess fat around the hips and trunk and perhaps an associated amenorrhea. It is not so well known, as Greenhill points out, that fat in these parts is common in every case of obesity, and that menstrual difficulties, such as amenorrhea, hypermenorrhea or dysmenorrhea, may promptly disappear after weight loss, even without endocrine treatment.

One type of endocrine obesity is that considered to be due to pituitary deficiency. However, experimentally the removal of the pituitary actually causes loss of weight. Clinically also, in Simmonds' disease, where there is a destruction of the pituitary, emaciation is found. Froehlich's syndrome is also usually considered to be a disease of the pituitary. This condition is certainly diagnosed more commonly than it actually exists. Many young boys with undescended testicles and with fat on their hips, trunks, breast and mons veneris have been considered to have this disease without actual proof. Most of these patients become normal without any treatment whatever. The true Froehlich's syndrome is probably due to a disease of the hypothalamus rather than the pituitary. A true type of pituitary obesity is the so-called Cushing's disease or basophile adenoma of the pituitary. These patients are not remarkably obese, but their obesity is confined to the girdle region of the body and develops so rapidly that painful striae of the skin are formed. This disease is quite rare, and in addition to the moderate obesity, there are gonadal disorders, osteoporosis, hypertension and polycythemia. These serve to delineate this rare type.

The thyroid gland is seldom involved alone as a cause of obesity. In hypothyroidism fat is not greatly increased in the patient. Instead, there is a peculiar form of fluid present, as is evidenced by the term myxedema. There are, however, fat deposits on the neck and shoulder, but these are not

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extensive. It is often stated that the basal metabolic rate in obese patients is low, and therefore they have hypothyroidism. Greenhill [1] again points out that the basal metabolic rate as ordinarily determined is the total basal metabolism, and takes into consideration actively oxidizing tissues as well as the inactive tissues, such as fat deposits. Since in obese individuals these inert deposits predominate, they weight the basal metabolism in a negative direction. If we should calculate the basal metabolism on the ideal weight basis, most obese individuals would have high metabolic rates. This author points out the futility of giving thyroid to most of these patients, when their tissues are already burning at a high rate.

There are very few facts available to blame obesity on gonadal deficiency. True there are cases of excess fat about the buttocks and thighs that comes on after the menopause and ovariectomy, but unequivocal proof is lacking.

There are a few other exceedingly rare causes of obesity which will be grouped together. Some authorities say that all obesity may be due to increased water retention. The feeling at present seems to be that in every obese patient some water retention is present, but that this is not the sole, or for that matter, the most important cause of the obesity. Water retention is said to take place in females before the menstrual period, but this is a transient phenomenon. However, in the treatment of any case of obesity this must be taken into consideration. Another cause, which must be extremely rare, is a lack of ketogenic hormone of the anterior pituitary. It is postulated that in this condition there is a disturbance in the transportation of fat. The fat is swept into the depots and deposited there, and there is great difficulty in mobilizing it again. Another extremely uncommon cause which is said to exist in patients with tumors near the pituitary, encephalitis, chorea or certain forms of brain injury is probably due to injury to the hypothalamus. Here also there may be a deficiency in the nervous control of the fat mobilizing mechanism.

Usual Causes of Obesity. We come now to the most common cause of obesity, i.e., exogenous obesity, or that due to overeating. It must be repeated again that the fat distribution and gonadal difficulties of an obese person might simulate an endocrine obesity, but most cases are actually due to gluttony. Even though we know the actual cause of most types of overweight, it is another matter to discern why these people overeat as they do. In many cases at least, overeating may be due to a psychic disturbance in which the individual is unprepared to meet the social demands of everyday life. Thus overeating is indulged in and obesity results. Bruch [2] has done a great deal of work on this subject in children. She has found that many overweight children are unhappy and maladjusted. Glandular treatment under these conditions is not only useless but harmful. The treatment is psychotherapy and diet. Greenhill [1] goes more deeply into the social, economic and psychic factors that cause people to overeat. An individual may have grown up in an environment where a great deal of food is eaten. He thus continues this practice of gluttony in later life, and the consequence is

overweight. The overeating may be an escape mechanism for a mental conflict. There is also a group of people who lack normal interests in life and obtain pleasure in overeating. It is often impossible to appease their appetites because they are unable to satiate their sensory desires (Anhedonism). Another form of mental conflict considered important in females is that obesity can be an escape from competition for masculine attention. In this condition overeating is an excuse. It can thus be seen that in addition to any treatment outlined, psychotherapy, especially of the family-physician type, must also be used in conjunction with any form of treatment. It can also be seen why such divergent reports appear in the literature on any form of treatment. It is impossible to formulate statistical results on these patients because of the psychic elements involved, and because of the varying abilities of different investigators in performing psychotherapeutic treatment.

Dietary Treatment. The first and foremost principle in the treatment of obesity is the placing of the patient on a low calorie diet. If this can be adhered to, no other treatment is required. However, in view of the psychic elements previously mentioned, this is often impossible alone. First, we have to show these patients how they will benefit by the reduction of weight. In young girls one has to point out the value of an attractive figure, and in older patients one must show how obesity causes damage to the cardiovascular system. As stated, the most important thing is to lower the level of food intake below the amount that is necessary to maintain the body weight. It will be the object of this paper to show how this can be done in many patients. During the course of treatment we must aim at the cultivation of new food habits in these patients, if our treatment is to have permanent value. We must also analyze the psychological causes of overeating and explain these to the patient.

In extreme obesity, Strang et al.[3] prescribed a diet adequate in proteins, vitamins and salts, but low in fats and carbohydrates. This diet consisted of about 550 calories per day, and under this régime, the subjects lost about 6/10 of a kilogram per day, over approximately a 60 day period. In this extremely low carbohydrate diet, the urine must be tested for acetone frequently. The partial starvation reduces weight, but since the fat stores are mobilized without adequate intake and burning of carbohydrates, acidosis may supervene. If the patient is less obese, a more liberal diet is prescribed which may go as high as 1,500 calories, but in our experience it is wise to limit it to from 1,000 to 1,200 calories. Good foods to include in such a diet are lean meats, egg white, fresh or skimmed milk, bran muffins, 5 per cent vegetables and flavored gelatin and citrus fruits. If three to five per cent vegetables are cooked in water several times, and the water thrown away, this will provide bulk with very little carbohydrate. Mayonnaise made with mineral oil is a good salad dressing which is fat-free, as far as the metabolism of the organism is concerned. Fat-free broth or bouillon is filling and is of negligible caloric value.

Overweight individuals should be told that they must absolutely avoid the following foods:

1. Mayonnaise, olives, olive oil, fatty meats, fried foods, gravy, chocolate, cocoa, ice cream and cream.
2. Pastries, macaroni, sodas, alcoholic drinks, canned fruits with syrup, sweet potatoes, and white cereals such as rice and farina.

The patient must eat very sparingly of the following fruits and vegetables: green peas, lima beans, potatoes, baked beans, corn, raspberries, apples, cherries, plums, bananas, prunes and grapes. These are the "15–20 per cent fruits and vegetables." The individual should also have a very limited intake of bread and butter. The patient may eat liberally of the following foods which have only a 1 to 5 per cent carbohydrate content.

Abbreviations Used in Figures

B. Benzedrine sulphate in milligrams
A. Atropine sulphate in fraction of a grain
T. Thyroid in grains
D. Desoxyephedrine in milligrams
G. Gels, such as metamucil, one teaspoonful in orange juice.
M. Mercupurin or mercuhydrin, one to two cubic centimeters intravenously.
Am. Aminophyllin in 3 grain coated tablets

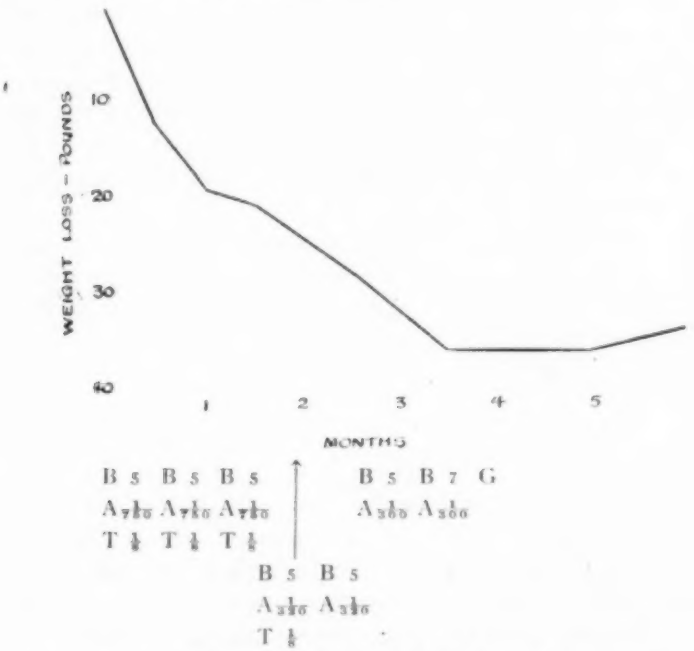

FIG. 1. C. M., f., age 32, weight 192 pounds, height 63 inches, optimum weight 140 pounds. Basal metabolic rate was minus 12. Weight gain was marked since birth of a child two years ago. Attempted to lose weight on 1,000 calorie diet and 1 grain of thyroid t.i.d., but without success, even though this was continued for six months. Weight reduction on appetite control therapy was adequate.

They are: lettuce, asparagus, spinach, beet greens, dandelion, water cress, cabbage, brussels sprouts, kale, leeks, broccoli, celery and swiss chard. A very good fruit is watermelon which has a small carbohydrate content. The patient should be cautioned against the use of too large quantities of water along with large amounts of salt. Even though water per se will not cause a weight gain, if it is taken with a sufficient quantity of salt, edema may result.

Methods of Controlling Appetite in Obese Patients. It has been found by experience, that merely admonishing a patient to adhere to a low calorie diet has been largely unsuccessful. This has been true even though the

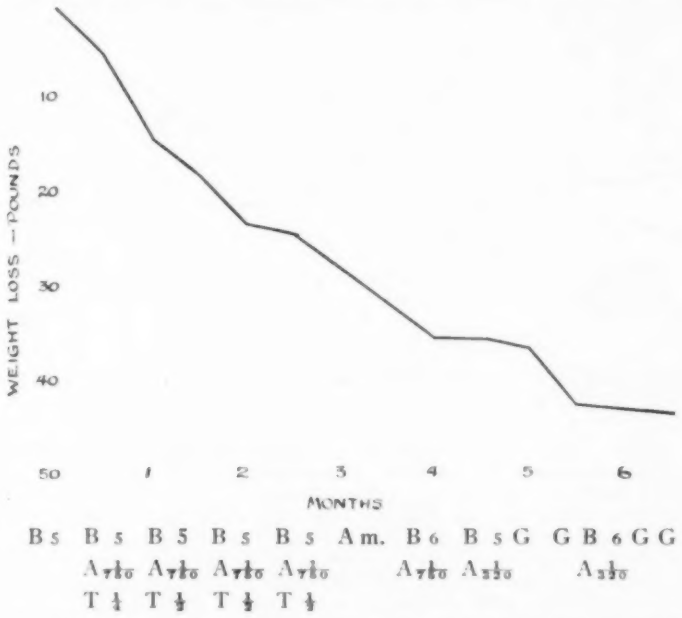

FIG. 2. A. McC., f., age 48, weight 218 pounds, height 69 inches, ideal weight 163 pounds, basal metabolic rate minus 8. Weight gain was marked in past six months. In addition this patient complained of tiredness, soreness of tongue and numbness of the fingers. She had previously had an enlargement of the thyroid for which she was given a half grain thyroid tablet three times a day. Subsequently she had been on a 1,000 calorie diet and thyroid 1 grain three times a day, without loss of weight. Diet plus appetite control therapy caused an adequate loss of weight.

patient may be sincere in his attempt to lose weight. This is because adherence to a low calorie diet alone will often cause intense weakness. This may be present even though vitamin and iron medication is included. For this reason it is necessary to employ means that will curtail the appetite and at the same time would give the patients a feeling of well-being that will encourage him to continue the dietary treatment. The appetite depressants (used in this study) were benzedrine sulphate (racemic amphetamine) and atropine. The dosage of benzedrine was usually started at 5 milligrams three times a day, and increased slowly at two week intervals to about 10

milligrams three times a day. Occasional cases required 12 milligrams three times a day. This substance was combined with atropine, in doses starting at 1/750 of a grain and gradually increased to 1/250 grain. These drugs were given together in a capsule one hour before each meal. A tolerance was soon developed for each of these drugs, so that the same dose would no longer cause a reduction in appetite. It was necessary, therefore, to increase the dosage of either or both of them, about every two weeks. Thyroid was included if the basal metabolic rate was below minus 5 per cent. The dose of thyroid which, when used, was also included in the same capsule, ranged from ⅛ of a grain to 1 grain three times a day. The appetite depressing medication was found to work best when taken about one hour before meals.

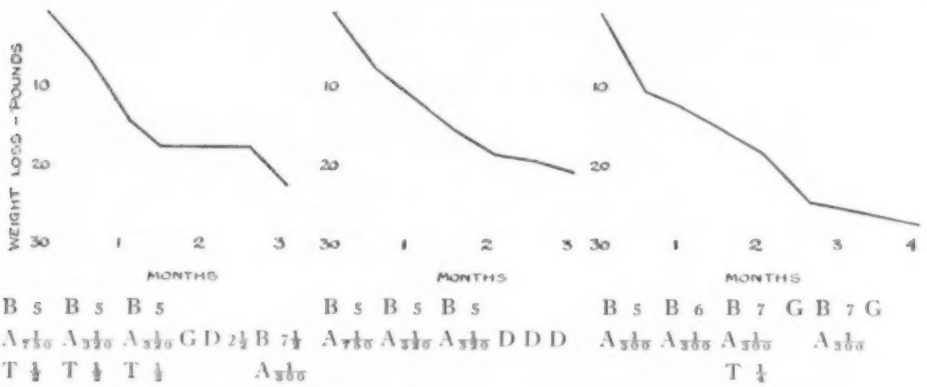

FIG. 3. (left) J. T., f, age 27, weight 158 pounds, height 66 inches, ideal weight 140 pounds. Patient complained of irregular menstruation, swelling of feet and headaches. These headaches were usually over one eye and occurred before or after her period. Basal metabolic rate was minus 12. In addition, she complained of occasional breaking of her finger nails. She had gained 20 pounds in the past four months, and volunteered that she could stand a great deal of heat. She was tried on 1,000 calorie diet and three grains of thyroid a day. This was ineffectual in causing a loss of weight, although some of her symptoms improved. Coincident with the loss of weight on the new therapy, her periods became normal and swelling of feet disappeared.

FIG. 4 (*center*). M. M., f., age 36, weight 151 pounds, height 63 inches, ideal weight 132 pounds, basal metabolic rate was just average normal. The patient's chief complaint was migraine headache and moderate amount of overweight. During her period of weight loss and dietary restriction, her headaches were few. This was probably due to restriction of certain foods to which she was sensitive. Weight loss was adequate on appetite control therapy.

FIG. 5 (*right*). T. S., f., age 40, weight 171 pounds, height 65 inches, ideal weight 146 pounds, basal metabolic rate was just average normal. Her complaints were pain in her legs, nervousness and obesity. She could not take thyroid without feeling light headed. Her previous attempts at weight reduction on diet therapy proved ineffectual and were abandoned easily. The appetite control therapy resulted in adequate reduction of weight, which has since been maintained.

Most women did not lose weight around their menstrual periods. This is a well known concept and is undoubtedly due to retention of water at that time. Under such conditions, aminophyllin in 3 grain tablets was given three times a day, to tide over the period of fluid retention. This often caused a satisfactory reduction of weight. Occasionally mercupurin or mer-

cuhydrin, a new mercurial, was used if aminophyllin was found to be ineffective.

It was invariably found that even though weight loss had been satisfactory for several months, a point was reached when the patient became refractory to both benzedrine and atropine. This is a phenomenon that has been noted with most patients receiving these autonomic drugs. Under these conditions, it was necessary to discontinue the medication. In order for the subject not to increase his weight again, it was decided to have the

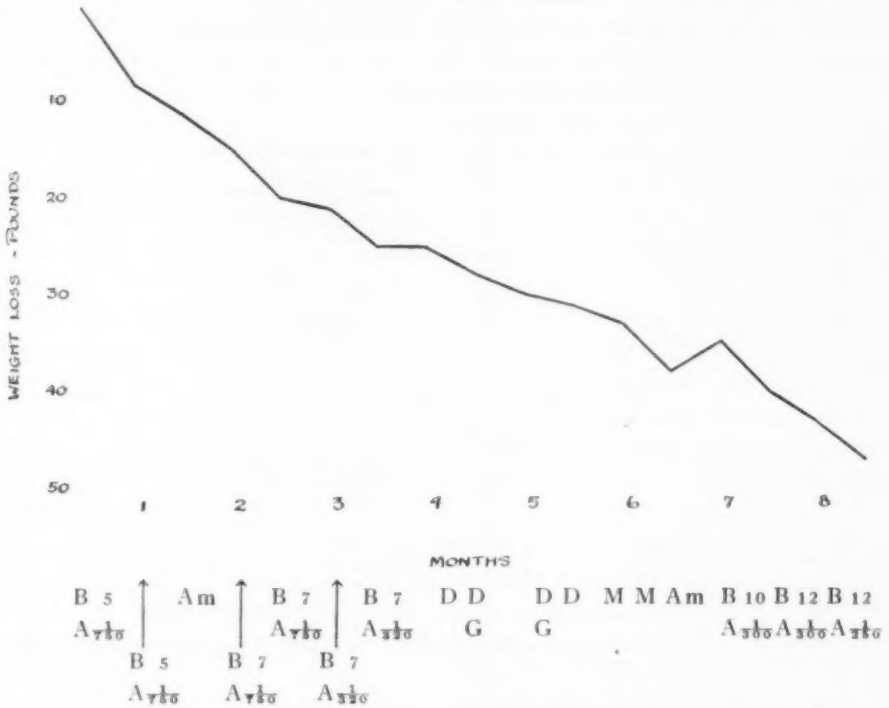

FIG. 6. C. W., f., age 44, weight 270 pounds, height 64½ inches, ideal weight 145 pounds, basal metabolic rate was just average normal. This patient complained of getting tired easily and marked obesity. She has been overweight for the past 20 years, when her weight was 190 pounds. Several previous attempts at weight reduction had failed. At the start of therapy, her pulse rate was 112, blood pressure 160 mm. Hg systolic and 90 mm. diastolic. Under the appetite control medication her blood pressure fell to 130 mm. Hg systolic and 90 mm. diastolic and pulse rate decreased to 96.

patient take a gel producing substance, such as metamucil, one teaspoonful in water or orange juice, immediately before eating. Although this did not reduce the appetite sufficiently to cause a loss of weight, except occasionally, it was able to tide the patient over a period of refractoriness to the appetite control drugs. After a period of two weeks the autonomic drugs could be resumed again, in smaller amounts, with adequate control of appetite.

Several patients were also tried on desoxyephedrine in doses of 2½ milligrams three times a day. This produced in some cases a satisfactory

ILLUSTRATIVE DIET LIST [1]

Your total calories should not exceed ..... for each day. Divide them as directed below. *Do not eat between meals.* Some exercise must go with this diet daily.

BREAKFAST:

You may select from below ..... calories.

	Calories		Calories
1/2 medium orange	25	1/2 cup cornflakes	50
1/4 small grapefruit	20	The average glass of milk	125
3 cooked prunes	45	1 glass of skimmed milk	70
1 teaspoon butter	50	1/2 tablespoonful heavy cream	35
1/2 cup oatmeal	75	1 teaspoon sugar	25
1/2 cup of cream of wheat	75	1 Uneeda biscuit	20
1 slice rye or white bread	50	Tea or coffee with no sugar	0

LUNCH:

You may select from below ..... calories.

	Calories		Calories
8 small asparagus tips	20	3/4 cup cooked cabbage	25
2/3 cup brussel sprouts	20	1/2 cup eggplant	25
3 stalks fresh celery	15	2 small green peppers	25
10 slices cucumber	15	1/2 cup stringbeans	25
1/4 small head lettuce	15	1 medium fresh tomato	20
1/2 cup cooked spinach	30	3/4 cup carrots	40
1/2 cup canned tuna fish	50	3/4 cup turnips	35
1/2 cup canned salmon	100	1 small apple	55
1/4 cup cottage cheese	65	1/2 cup muskmelon	40
1 slice rye or white bread	50	Tea or coffee with no sugar	0

DINNER:

You may select from below ..... calories.

	Calories		Calories
1 cup vegetable soup	75	2 slices roast veal	80
1 cup spinach soup	85	1 slice breast chicken	60
1 cup beet soup	90	1/2 small chicken broiler	75
2 slices lean roast beef	85	1 egg	75
2 cakes hamburger steaks	85	1 piece 2 x 3" Haddock	35
1 portion lean round steak	85	6 large oysters	40
2 slices lean roast lamb	95	1 piece brook trout	45
1 slice rye or white bread	50	Tea or coffee with no sugar	0

Bread, beverages, fruit, etc. from the above list, may be added to any meal provided the total calories do not exceed the amount prescribed.

THE FOLLOWING FOODS MUST BE AVOIDED:

Nuts, olives, olive oil, chocolate and cocoa, gravy, cream soups, sauces, ice cream, candy, pastry, macaroni, potatoes, alcoholic beverages, canned fruits in syrup, and highly spiced and salted foods. Do not use sugar unless you absolutely have to.
Four glasses of water each day are allowed. Be sure that your daily menus include a fresh fruit, either meat, fish or egg, milk and three vegetables.

appetite reduction which, however, continued only a short period of time. In most cases, side actions were too marked to advise further use of this drug, and it was therefore discontinued.

Case Records. This report covers 150 privately treated cases of obesity. It was found that these private patients were better subjects, because most of them genuinely wanted to lose weight. There was also more time to study the possible psychic causes for the obesity, and an attempt made to treat them with a certain amount of psychotherapy. The study has been continuing for the past one and a half years. It has been almost uniformly

successful, although seven absolute failures were encountered. Some of these occurred at the outset of the project when very small doses of the substances were used. As experience was gained with the use of these drugs, it was found that only rarely was a rise in blood pressure or pulse rate seen. Thus, it is obvious why opinion on the value of these drugs varies so much, and why statistical analysis does not give an accurate picture. Each patient requires an individual dose of each drug, and also requires an increase at a different rate. Some psychotherapy is also required in the case of each patient, either during the treatment, or certainly after the treatment is discontinued. New eating habits must be established if a patient is not to regain his lost weight. All the female patients require some form of diuretic therapy during, and often following, the menstrual period. All the patients develop a refractoriness to the therapy, and therefore require a short period of rest. We have used the gel treatment in this interval. This same substance is usually required for some period after satisfactory weight loss has been reached, and until new eating habits have been thoroughly established. If this does not occur, the whole treatment has been wasted (figures 1–6).

Possible Mode of Action of the Drugs Used in This Study. A. Benzedrine. Many authors have reported that benzedrine sulphate reduces appetite. At first it was accidently discovered during its use for central nervous system stimulation.[5, 6] Subsequently it was used for this definite purpose. The theories of its action are many, and vary with the different authors. We feel, however, that its action is definite. These actions are said to be as follows:

1. Stimulation of motor activity.[5, 6, 7] This action certainly could not be the most important one, because under such conditions food intake would be proportionately increased, which would defeat the purpose of the drug.

2. Slowing of digestion.[8, 9, 10] It has been shown that benzedrine sulphate delays emptying time of the stomach [11, 12] and often decreases intestinal peristalsis.[13] However, the depression of appetite is often present with doses too tiny to cause delay in stomach emptying time and a decrease in peristalsis of the intestinal tract.[8, 9]

3. Improvement of mood. It has been noted that apathetic obese patients often overeat because of the impairment of satisfaction of their sensory desires.[7, 9, 10] This has been explained elsewhere in this paper. Often these patients respond dramatically to benzedrine and the other synergistic drugs used. The increased mental activity might conceivably distract the patient from an inordinate desire to satisfy his reactions by the intake of food.

4. Metabolic effect. Some authors [14] attribute weight loss in benzedrine treated cases to an increase in the basal metabolic rate. This has been largely repudiated. In our own series, when benzedrine and atropine were taken without thyroid, there was no rise in the basal metabolic rate.

5. Water retention. One author [9] suggested that the initial weight loss (with benzedrine) might be due to inhibition of water retention, since benzedrine seems to induce a loss of weight even when the caloric intake was increased. There is some justification for this theory in several cases in our series. When combining a mercurial diuretic by injection with benzedrine by mouth a more impressive weight loss occurred than by using the mercurial alone or in combination with the gel.

6. Hypothalamic stimulation. Bruch [15] stated that since benzedrine is supposed to be a hypothalamic stimulant, it might be reasonable to suppose that it affects fat metabolism as well as appetite by way of the hypothalamus. It has been assumed to act directly on the appetite center.

Occasional reactions may occur, including headache, restlessness, insomnia, irritability, palpitation and a disturbance of the bowel habit. However, it is necessary to state that these reactions are exceedingly few, and are merely mentioned to call attention to their rarity. It has been necessary only in a few cases to add phenobarbital at night because of insomnia. It was not found that the treatment resulted in an increase in blood pressure. Contrariwise it was often noted, as Rosenberg [8] has stated, that the high blood pressure usually fell in proportion to the weight loss. It was found that the atropine sulphate in the capsule would counteract some of these reactions, because they were exceedingly infrequent when the combined therapy was used. Because of the relaxing effect of the drugs on intestinal musculature, constipation usually resulted and a mild laxative was advised.

The patient must be put on vitamin-mineral supplements as soon as therapy is started, because his dietary intake will often be erratic. In practice, the patient is put on at least one potent pan-vitamin capsule, along with two ferrous sulphate tablets in 3 to 5 grain dosage. It was found that these preparations are best given at night, so as not to confuse the patient.

B. Atropine: Atropine as an appetite depressant has recently been popularized by Greene.[17] This author employed belladonna alone, and in combination with phenobarbital in a series of 25 patients to control the appetite. This drug was first used for this purpose by Franke [18] in 1913. He found that atropine in the form of belladonna, 15 drops of the tincture, given three times a day, 15 to 20 minutes before meals, resulted in appetite depression. At the end of his article this author posed the question whether belladonna merely has a sedative effect on the stomach, or whether it also inhibits the gastric secretion and perhaps also affects the musculature of the stomach. The answers to these questions are still not entirely known.

C. Gels [19]: It was found necessary to use something that would mechanically decrease the amount of food ingested when the patient became refractory to the appetite depressing drugs. For this purpose one of the gels, metamucil, was used, one teaspoonful being dissolved in a glass of water or orange juice three times a day, taken immediately before meals. Although in some few cases, this resulted in an actual diminution in the intake of food and a further loss of weight, the usual result was merely a

lack of weight gain. This was a very useful phenomenon. During this period, usually about two weeks, when these gels were used an apparent letdown of mood occurred, in which the patient did not feel as strong as he had previously felt. This period was also a good time in which to stress the value of new food habits.

D. Diuretics: For reasons already sufficiently discussed, most patients require a diuretic during their course of treatment. For this purpose aminophyllin in 3 grain coated tablets was used. If, in a week, this was unsuccessful in causing a further loss of weight, either mercupurin or mercuhydrin was given. These preparations were usually given in 1 or 2 c.c. doses intravenously. In some cases, the diuretic effect was increased by continuing the benzedrine during the period of diuresis. Of course, urine examination was done before and after the mercurial therapy. In no case was there a change noted in the urine. It was also necessary to give mercurials in male patients. There must be water retention in probably every case of obesity, either male or female, although it is not of a cyclic type in the former.

Diet. The patient should always be given a diet of about 1,000 calories. This will probably not be exceeded during the period of the use of the autonomic drugs. However, the patient should have a diet list to refer to during the period of refractoriness to the drugs and for guidance in the formation of a sound habit. A diet list [4] such as is given to my patients is included here. The calories may be divided as follows: 150 for breakfast, 250 for lunch and 600 for dinner. This may be varied according to the patients.

Exercise. Exercise is of benefit in the management of the obese patient for two reasons. One is for the general stimulation of motor activity which occurs during exercise, and the other because exercise helps the patient reduce in certain areas that the patient desires. These exercises may also include massage, and other passive types of exercise, but it should be realized, as Newburgh [20] points out, that the muscular activity indulged in by the attendant is incapable of increasing the heat production of the patient. The patient must do the work, if he is to dissipate the energy. Exercise alone is usually not sufficient to cause an adequate loss of weight, and is a much harder way of reducing than by limitation of food intake through appetite depression.

Summary

The causes of obesity are discussed at some length. It was found that the most important cause of overweight is overindulgence of food. Several ways of reducing the appetite have been found effective in the treatment of 150 patients over a period of one and a half years. In order to achieve permanent results, the patient must be shown the reason for his obesity and the advantages that weight loss would give him. There must

also be an attempt to create new food habits so that the loss of weight may be permanent.

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EVALUATION OF THE ERYTHROCYTE SEDIMENTATION TEST IN LEPROSY: STATISTICAL STUDY OF MORE THAN TWO THOUSAND TESTS IN MORE THAN FIVE HUNDRED PATIENTS *

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THE changes in the erythrocyte sedimentation test which occur during the course of leprosy have not been studied as thoroughly as they have in tuberculosis. Although this laboratory procedure has been employed in both diseases for approximately the same period of time, it has met with great popularity in tuberculosis whereas comparatively few articles on the subject are extant in the literature on leprosy. Not all investigators are in accord as to the significance of this test in leprosy. Many, including Landeiro,[1] Muir,[2] and Schujman,[3] report that it bears a close relationship to the type of disease, being rapid in the lepromatous (nodular) and mixed types and often approaching normal in the neural form. Some writers, Muir [4] and Kerr,[5] find special use for the sedimentation index as a test of the patient's tolerance to medication, particularly his reaction to the iodides.

PRESENT STUDY

The present report is based upon 2023 erythrocyte sedimentation tests made on 510 patients with different types of leprosy at the National Leprosarium. The period of observation varied from eight months to four years. The 510 patients were divided according to sex into 338 males and 172 females. Their ages varied from six to 82 years, the great majority being between 20 and 40 years.

The patients were classified as to types of disease into 384 lepromatous or mixed cases, 108 neural cases and 18 tuberculoid cases. The lepromatous and mixed cases were classified together for greater convenience, as it was difficult at times to separate them clinically. There were many borderline cases that might have been included in either group, depending upon the thoroughness of the neurologic examination. Also, during the prolonged period of study the disease frequently changed from the lepromatous to the mixed type. Since it is the lepromatous lesions which carry the grave prognosis and the superimposition of neural lesions is of little added consequence, it would have served no useful purpose to separate the mixed from the lepromatous cases.

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Technic

The technic used in this study was the Cutler sedimentation test modified only by the substitution of oxalates for sodium citrate as the anticoagulant. The proportion of potassium and ammonium oxalates used (4 mg. of potassium oxalate and 6 mg. of ammonium oxalate for 5 c.c. of blood) is that recommended by Heller and Paul [6] as giving minimal shrinkage of the erythrocytes. This anticoagulant is advocated also by Kolmer and Boerner [7] and Wintrobe and Landsberg.[8] It proved entirely satisfactory at the National Leprosarium. An additional advantage was that the same sample of blood could be used for blood chemistry. In a series of duplicate sedimentation tests on a group of patients, using 3.8 per cent sodium citrate for one test and the potassium and ammonium oxalates for the other, the writer obtained closely comparable results.

Relationship of Sedimentation Test to Type and Extent of Leprosy

The erythrocyte sedimentation test is at best a crude laboratory procedure. Nevertheless, within certain limitations, it has a practical value as an estimation of the amount of tissue destruction which is taking place in the body. Muir [4] asserts that "uncomplicated leprosy, however heavy the infection, does not of itself accelerate sedimentation." This was not the experience at Carville. In this leprosarium, on the contrary, uncomplicated leprosy, even when the general health of the patient was otherwise good, produced a rapid sedimentation. This occurred in all types of leprosy, although to a greater

Table I

Distribution of Total Erythrocyte Sedimentation Tests Among the Different Types of Leprosy

Type of Disease	Sedimentation rate in mm. at the end of an hour (Cutler)								
	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40+	Total
Tuberculoid	14	8	7	6	7	4	0	0	46
Neural	54	88	107	121	90	14	5	0	479
Lepromatous and mixed	20	35	82	208	575	441	116	21	1,498
Total	88	131	196	335	672	459	121	21	2,023

extent in the lepromatous and mixed cases. Even patients with arrested leprosy of a number of years' duration seldom had normal sedimentation records. Leprosy is classified as arrested at the National Leprosarium only after a patient has had bacteriologically negative skin and nasal smears for 12 consecutive months and is declared free from clinical evidence of activity by a medical parole board.

Occasionally, sedimentation indices approaching normal were encountered in patients with minimal or discrete lesions, whether of the lepromatous or neural type. Thus, although tuberculoid and neural cases as a group had

slower blood sedimentation rates, in individual cases the extent as well as the type of the disease exerted an influence on the test. Very exceptionally, patients with far advanced disease for some unknown reason showed normal sedimentation tests. These paradoxical findings occurred in three patients at the National Leprosarium. In each instance, a repetition of the test after several months had elapsed resulted in a reversion to an abnormal zone more consistent with the patient's condition.

Table 1 shows the total number of sedimentation tests made at the National Leprosarium, distributed according to the type of the disease and without regard to the individual patient.

Table 2 shows the average sedimentation index of all tests made on each of the 510 patients. The patients are classified according to the type of the disease. Both tables demonstrate, but table 2 more clearly, that the sedimentation rates increase in order from the tuberculoid to the neural and finally to the lepromatous and mixed types of leprosy. In a supplement to table 2 the definite effect of trophic ulcers in increasing the sedimentation indices of neural cases is shown.

TABLE II

Average Sedimentation Index of Leprosy Patients Classified According to Types of Disease

Types of Disease	Sedimentation rate in mm. at the end of an hour (Cutler)								
	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36+	Total
Tuberculoid	5	4	2	5	1	1	0	0	18
Neural	5	19	28	31	21	3	1	0	108
Lepromatous and mixed	0	7	12	48	151	131	28	7	384
Total	10	30	42	84	173	135	29	7	510

TABLE II–X

Average Sedimentation Index in Neural Cases with and without Trophic Ulcers

	Sedimentation rate in mm. at the end of an hour (Cutler)								
Neural cases with large trophic ulcers	0	0	1	3	12	3	1	0	20
Non-ulcerated neural cases	5	19	27	28	9	0	0	0	88

Table 3 shows the average sedimentation rates of the 510 patients classified as to extent of the disease in its different types. It demonstrates that the stage of advance of leprosy exerts a definite influence upon the acceleration of sedimentation of the red blood cells in every type of the disease.

Table 4 gives the sedimentation tests in bacteriologically negative as compared with bacteriologically positive cases of leprosy. In 79 per cent of negative cases the sedimentation rate was less than 20 mm., whereas in 78 per cent of positive cases it was more than 20 mm.

TABLE III

Average Sedimentation Index in Relation to Stage of the Disease

Type	Stage of Disease	Sedimentation rate in mm. at end of an hour (Cutler)									Type Grand Total
		0–5	6–10	11–15	16–20	21–25	26–30	31–35	36+	Total	
Tuberculoid	Minor	5	4	1	1	0	0	0	0	11	
	Major	0	0	1	4	1	1	0	0	7	18
Neural	Minimal	4	10	8	3	0	0	0	0	25	
	Moderately advanced	1	9	17	20	7	0	0	0	54	
	Far advanced	0	0	3	8	14	3	1	0	29	108
Lepromatous and mixed	Minimal	0	7	6	6	8	0	0	0	27	
	Moderately advanced	0	0	6	41	125	35	2	0	209	
	Far advanced	0	0	0	1	18	96	26	7	148	384
Grand Total		10	30	42	84	173	135	29	7	510	510

TABLE IV

Average of Sedimentation Tests in Bacteriologically Positive and Negative Cases of Leprosy

Bacterioscopy	Sedimentation rate in mm. at the end of an hour (Cutler)								
	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36+	Total
Negative	6	16	19	30	14	3	1	0	89
Positive	4	14	23	54	159	132	28	7	421
Total	10	30	42	84	173	135	29	7	510

TABLE V

Average of Sedimentation Tests in Arrested Cases of Leprosy

	Sedimentation rate in mm. at the end of an hour (Cutler)								
	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36+	Total
Arrested cases	3	10	17	20	13	0	0	0	63

Table 5 shows the average sedimentation rates of 63 patients who have arrested cases of leprosy. In many of these patients the disease has remained arrested for more than one year and in a few for more than 10 years. It can be noted that 13, or only 20 per cent, are within or near the normal range. An equal number, on the contrary, are within the 21 to 25 mm. zone, generally considered as indicating disease activity. A considerable number of

the latter group have permanent deformities and mutilations resulting from the nerve destruction of leprosy. The results of the sedimentation test in arrested leprosy suggest that disintegration in the nerves or other tissues is probably still slowly progressing in latent leprosy.

Because, as a rule, the erythrocyte sedimentation rates do not revert to normal in arrested cases of leprosy, the value of this test is considerably limited in a leprosarium. The changes occurring in leprosy are very slow in development. The healing process, when it occurs, is of prolonged evolution. Consequently, changes in the sedimentation rates in patients with leprosy take place only after long intervals of time. For this reason, this test is of relatively less significance in leprosy than it is in tuberculosis where the healing and breaking down processes in the tissues are proportionally more rapid. It is also the writer's impression, from experience with both diseases,[9] that there is a relatively greater deviation from normal in leprosy than in tuberculosis when comparing minimal, moderately advanced and far advanced stages of both diseases.

Experience at the National Leprosarium showed that six months was usually a sufficiently short period between tests to record any information contributed by the sedimentation reaction in leprosy. This test was found to be generally not sensitive enough to predict improvement or aggravation in leprosy. Thus, it was usually too tardy to detect a patient's tolerance to new therapeutic procedures.

TABLE VI

Last Sedimentation Test Preceding Death by Less Than 6 Months

	Sedimentation rate in mm. at the end of an hour (Cutler)								
	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36+	Total
Deaths	0	0	0	3	8	28	22	14	75

Table 6 gives the last sedimentation test performed before death on 75 patients who died at the National Leprosarium. Most of the tests preceded death by three to six months. It will be noted that the sedimentation index of 88 per cent was more than 26 mm. and that of 48 per cent more than 31 mm. Since few patients except those approaching death ever attain such extremely high rates, the bracket above 30 mm. may be considered as the danger zone presaging death in leprosy.

Sedimentation Zones

Experience at the National Leprosarium has led to the classification of the sedimentation rates into various zones of different prognostic significance. It was found that patients whose blood sedimentation consistently fell within one of these zones showed a relatively more or less favorable reaction to the disease in comparison with those whose blood sedimentation was recorded in

higher or lower zones. Also, changes from one zone to another were an indication that the patient was improving or getting worse according to whether the sedimentation rates were rising or falling. After considerable experience, the following zones have been designated:

Zone 1, from 0 to 10 mm.—normal zone, or zone of arrest of leprosy.
Zone 2, from 11 to 20 mm.—zone of quiescence or slight activity of leprosy.
Zone 3, from 21 to 25 mm.—zone of moderate activity of leprosy.
Zone 4, from 26 to 30 mm.—zone of severe activity of leprosy.
Zone 5, from 31 to 40 mm.—danger zone, or death zone of advanced leprosy.

It was observed that in cases of leprosy in which repeated sedimentation tests were below 10 mm. or rarely rose into the second zone the prognosis was favorable and there was a tendency for the disease to become arrested. Such patients had minimal lepromatous lesions or had mild cases of neural or tuberculoid leprosy. A sedimentation index falling within the second zone signified that the patient was reacting fairly well to the disease and its treatment. These patients had slight cases of lepromatous or mixed leprosy or

TABLE VII

Classification of Patients into Prognostic Zones According to the Average of Their Series of Sedimentation Tests

Zones	Number of Patients	Percentage
Zone I, Normal (0–10 mm.). Arrested or quiescent disease, good prognosis	40	7.8
Zone II, Low (11–20 mm.). Slightly active or quiescent disease. Fair prognosis	126	24.7
Zone III, High (21–25 mm.). Active disease, guarded or poor prognosis	173	33.9
Zone IV, High (26–30 mm.). Very active and progressive disease or advanced disease. Poor prognosis	135	26.5
Zone V, Ultra high (31 mm. +). Far advanced active disease, terminal stage. Hopeless prognosis. Death near	36	7.1
Total	510	100

active neural or tuberculoid types of the disease. In the largest number of patients the sedimentation index was recorded in the third zone. These patients usually had moderately advanced disease of the lepromatous or mixed type with guarded prognosis. Occasional neural cases with large infected trophic ulcers or extensive mutilations were also in this group. Patients with sedimentations in the fourth zone had, as a rule, far advanced lepromatous leprosy with poor prognosis. Patients whose sedimentation ranged above 30 mm. were generally in the terminal stages of the disease and approaching death. Such patients seldom survived more than two years.

Table 7 shows the classification of the 510 patients into the different sedimentation zones according to the average of all the sedimentation tests made on them during the period of study.

Sedimentation Patterns

By now it must be evident to the reader that a single sedimentation test is of little practical value in leprosy. A series of tests made on the same patient during a long period, usually several years, is of some significance and may indicate the general trend of the course of the disease. From experience at the National Leprosarium it was learned that serial sedimentation tests on individual patients conformed to certain patterns. These different patterns were of four types, each suggesting a different mode of reaction to the disease. These four patterns have been designated as follows:

1. Horizontal sedimentation curve, prognosis dependent upon height of curve.
2. Irregular sedimentation curve, guarded prognosis.
3. Ascending sedimentation curve, poor prognosis.
4. Descending sedimentation curve, good prognosis.

Table VIII

Serial Sedimentation Patterns in Leprosy

Type of Serial Sedimentation Curve	Number of Patients	Percentage
Horizontal	137	49
Irregular	67	24
Ascending	47	17
Descending	28	10
Total	279	100

Table 8 shows the classification of 279 patients in whom four or more erythrocyte sedimentation tests were made during the course of two to four years into the above four patterns. It was found that in 137 of these patients, or 49 per cent, the sedimentation curve conformed to the horizontal type; in 67, or 24 per cent, it was of the irregular type; in 47, or 17 per cent, of the ascending type; and in 28, or 10 per cent, of the descending type.

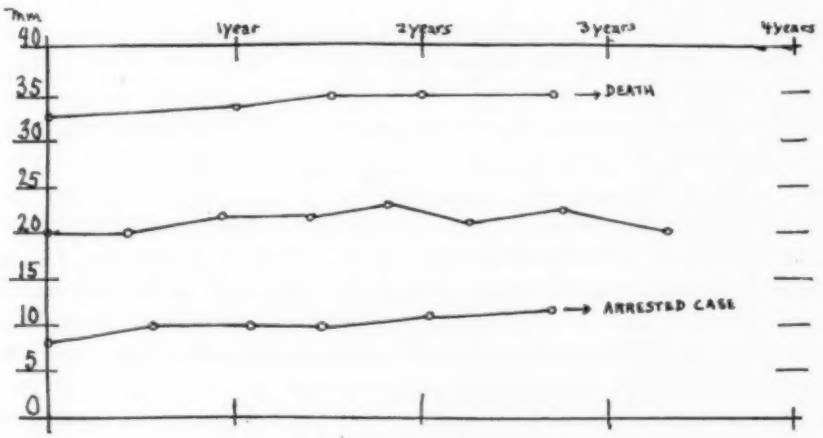

Fig. 1. Horizontal curves.

A horizontal or level curve usually occurred when the disease was stationary or showing little change during the course of years. A horizontal sedimentation curve of very high level, since it remained within an extremely abnormal zone, generally accompanied an advanced disease of unfavorable prognosis. When the horizontal pattern was in a low zone, approaching

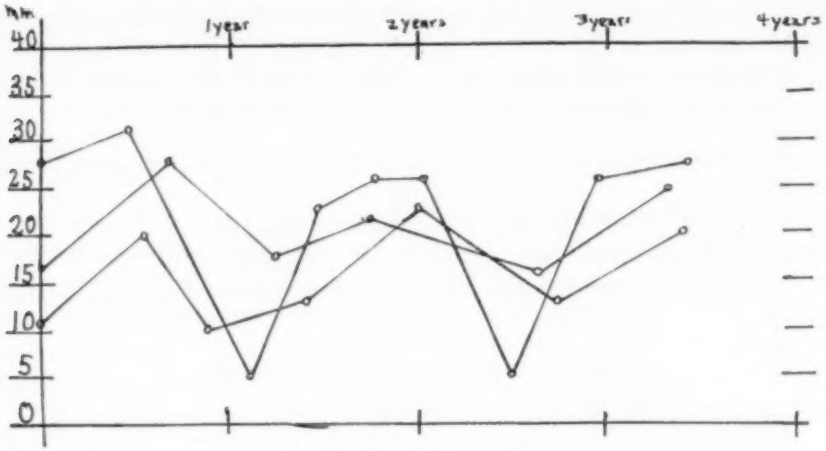

FIG. 2. Irregular curves.

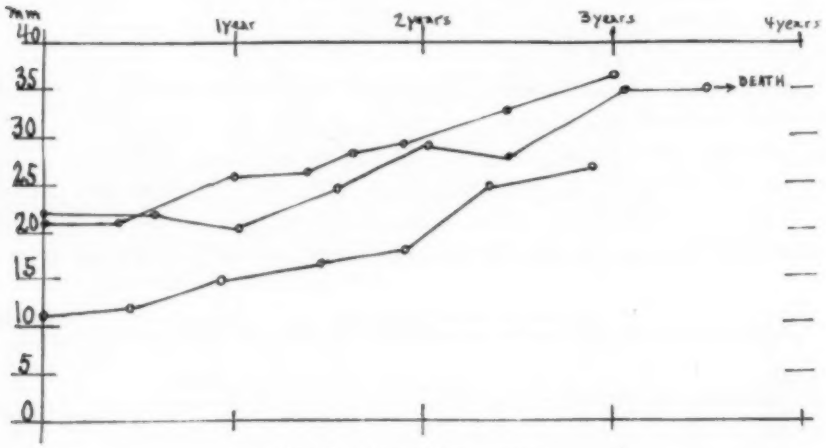

FIG. 3. Ascending curves.

normal, it was usually associated with minimal disease or with a neural type of good prognosis. Horizontal curves of intermediate zones were of corresponding prognostic significance. Figure 1 illustrates horizontal curves of different levels in three individual cases of leprosy of different severity. The patient with the consistently high sedimentation is now dead, whereas the one in the low zone is at present an arrested case.

Patients with irregular or bizarre sedimentation curves had guarded prognosis. Peaks in such curves were commonly due to severe complications,

intercurrent diseases, or acute leprae reactions. The valleys resulted from temporary remissions in the disease, healing of ulcerations or unknown causes. Figure 2 illustrates the bizarre sedimentation curves of three patients.

An ascending sedimentation curve, as a rule, indicated a disease which was progressing unfavorably. Figure 3 illustrates three such curves among the patients at the National Leprosarium. In one case death was the outcome.

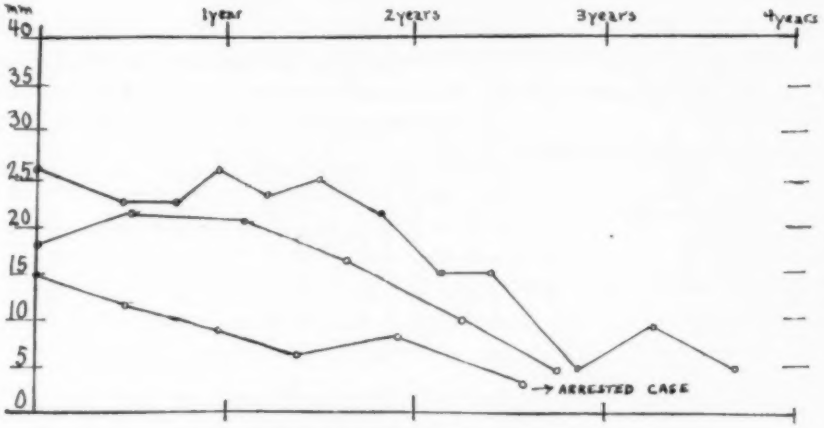

FIG. 4. Descending curves.

A descending sedimentation curve usually accompanied improvement and suggested a favorable prognosis. Figure 4 demonstrates such curves in three patients. In one case leprosy became arrested.

EFFECTS OF COMPLICATIONS AND INTERCURRENT DISEASES UPON THE SEDIMENTATION TEST

Intercurrent diseases and the severe complications of leprosy were found frequently to have an accelerating effect upon the sedimentation rate. Experience at the National Leprosarium was that intercurrent diseases, such as tuberculosis, malaria, syphilis, malignancy and others, had relatively less potent effect upon the sedimentation reaction in leprosy than had the serious complications of the disease. Tuberculosis complicating leprosy did not seem seriously to alter the settling velocity of the red blood cells. Malignancy likewise did not seem unduly to accelerate the reaction; the few patients dying of malignancy had lower rates of blood sedimentation than those dying of leprosy without malignancy.

Nephritis and secondary anemia caused considerable increase in the red cell sedimentation rate in leprosy. It was felt that leprosy as a systemic disease in its dissemination throughout the body was directly or indirectly responsible for these two pathologic conditions. They developed, in the

majority of cases, in the advanced or terminal stage of leprosy. Leprous ulcerations, both mucosal and cutaneous, and trophic ulcers have a great accelerating influence on the rate of settling of the erythrocytes. This was particularly true when there was secondary pyogenic infection, which was the rule rather than the exception in leprous ulcerations. Acute leprae reactions also caused a temporary rise in the sedimentation index, which generally lagged in returning to its prior level after the febrile reaction and skin eruption subsided.

TABLE IX

Effects of Complications and Intercurrent Diseases upon the Sedimentation Index in Leprosy

Complicated and intercurrent diseases	Sedimentation rates in mm. at the end of an hour (Cutler)								
	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40+	Total
Leprous and trophic ulcers	0	0	0	2	12	36	15	1	66
Leprous laryngitis	0	0	0	0	1	15	6	0	22
Nephritis	0	0	0	0	1	9	17	11	38
Acute leprae reactions	0	0	0	2	23	27	7	0	59
Tuberculosis	0	0	1	3	5	9	2	0	20
Malignancy	0	0	0	2	2	4	1	0	9

Table 9 records the sedimentation indices of patients with severe complications or intercurrent diseases. It can be seen that such complications of leprosy as leprous and trophic ulcers, leprous laryngitis, nephritis and acute leprae reactions had a greater effect in lessening the suspension stability of the erythrocytes than had such intercurrent diseases as tuberculosis and malignancy.

Figure 5 depicts the effect of acute leprae reactions and the subsequent

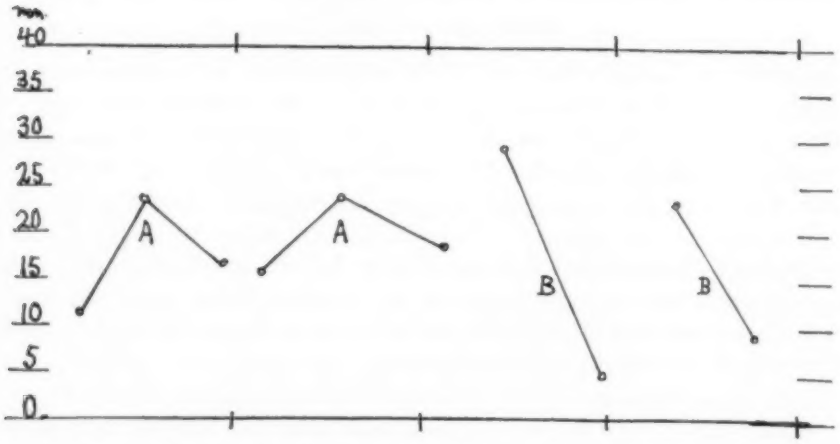

FIG. 5. Changes in sedimentation due to (A) acute leprae reactions, (B) healing of ulcerations.

recovery therefrom upon the sedimentation test. It also shows the beneficial effect of healing large infected leprous and trophic ulcers.

Correlation between Hyperglobulinemia and Rapid Sedimentation in Leprosy

The erythrocyte sedimentation test may be considered as a gauge of the amount of the products of tissue destruction which are absorbed into the blood stream. These tissue products are not exactly known but are probably represented in the protein portion of blood plasma. It has been repeatedly demonstrated that the causative agent of the sedimentation of the red blood cells is contained in the liquid portion of the blood and not in the erythrocytes. It is also known that the tissue changes in leprosy result in the absorption by the blood of abnormally large amounts of globulins. The writer believes that the same tissue changes which are responsible for the excessive accumulation of globulins in the blood in leprosy also account for the presence of the abnormal tissue products which result in increased erythrocyte sedimentation rates. It can be reasoned, therefore, that, depending upon the activity and the extent of the disease, there will be absorbed into the blood stream proportionate amounts of globulins and of tissue substances responsible for the rapidity of the erythrocyte sedimentation. It was thus considered interesting to study the content of serum globulin in relation to the speed of blood sedimentation in leprosy in the same samples of blood.

Table X

Correlation Between Serum Globulin and Sedimentation Test in Leprosy

Globulin content of blood	Sedimentation rate in mm. at the end of an hour (Cutler)				
	1–10 mm./hr.	11–20 mm./hr.	21–30 mm./hr.	31–40 mm./hr.	Total
Low, less than 1.7 per cent	2	2	2	1	7
Normal, 1.7 to 3.25 per cent	10	12	16	5	43
High, 3.3 to 6.2 per cent	1	19	42	15	77
Per cent of hyperglobulinemia	8%	58%	70%	71%	
Total	13	33	60	21	127

Table 10 shows the results of this comparison. The two laboratory procedures were carried out on the same blood samples in 127 patients with different types of leprosy. The normal range of serum globulin, from 1.7 to 3.22 per cent, is that given by Rowe [10] after a review of the literature. For convenience the cases were divided into three groups, those with low serum globulin, those with normal serum globulin and those with hyperglobulinemia. It is observed that the range of sedimentation coincides closely with the globulin content of the patient's blood.

Conclusions

The erythrocyte sedimentation test is found to be accelerated in all types of leprosy.

Although the greatest deviation from normal is encountered in the lepromatous and mixed cases, the sedimentation rate is also abnormal, with but few exceptions, in the neural and, to a less extent, in the tuberculoid type of the disease.

Even in patients with arrested leprosy of long duration, the test seldom is within the normal level.

Single sedimentation tests are of no practical value in leprosy, but repeated tests at six month intervals may indicate the trend of the disease and are of some prognostic significance.

At the National Leprosarium changes in the erythrocyte sedimentation index have been of slight clinical value as an estimate of the patient's reaction to any therapeutic measure.

It is found convenient to divide the sedimentation tests into five zones of activity and the serial sedimentation record of each patient into horizontal, irregular, ascending and descending curves, which carry different prognostic significance.

Although no claim is made that the factor responsible for the sedimentation of the erythrocytes is related to the globulin content of the blood, it is found that there is some correlation between the two conditions in patients who have leprosy.

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SYNCOPE ON EXERTION: RELATIONSHIP TO CORONARY ARTERY DISEASE*

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THE physician, realizing that syncope is most commonly not cardiac in origin, often gives it little weight in cardiac diagnosis, unless bradycardia or extreme tachycardia is present. Relationship to physical effort is an additional circumstance which should particularly draw attention to the heart for an explanation.

The term *syncope* implies loss of consciousness due to cerebral ischemia. The essence of such an attack, ischemia, implies an inadequate flow of blood to the brain and one would look for an explanation, according to Lewis,[1] in a deficient input of blood into the heart, of vascular origin, *precardiac* in the sense that some mechanism interferes with blood flow to the heart, or as the result of the failure of the heart to do its work adequately, a *cardiac* cause. To these possibilities and of great interest, especially from the standpoint of mechanism, must be added a third type, a temporary cerebral ischemia due to causes for impaired cerebral flow in the arterial tree peripheral to the heart, a *postcardiac* mechanism in that blood flow is disturbed after an adequate supply leaves the heart. Under such circumstances the explanation for cerebral ischemia is not always immediately evident, and in some instances of syncope of the postcardiac type ischemia is not the apparent cause.

The three groups thus divided upon the basis of mechanism would appear at first to solve the problem of differential diagnosis and separate syncope of heart disease from other types. Unfortunately, heart disease may be responsible for the vascular, or precardiac, type, as in the syncope associated with shock in myocardial infarction, as well as for the second and third varieties. Nor is it satisfactory to know simply whether syncope comes about or does not come about from heart disease, for the diagnostic implications and therapy depend as well upon the mechanisms.

In the precardiac type of syncope, a diminished supply of blood is presented to the heart. The following case report is a rather unusual example of this group.

Case 1. A. G., age 21, presented himself for examination because of attacks of syncope. These were preceded by vertigo and occurred chiefly on changing from the recumbent to the upright position. These attacks began six months before the initial examination and were associated with general weakness, loss of libido and constipation. The patient attributed his complaint to a severe bout of influenza which necessitated a prolonged period of rest in bed.

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Physical examination was entirely normal except for drop in blood pressure on sitting and standing. Blood pressure level when lying down was usually about 120 mm. Hg systolic and 84 mm. diastolic; on sitting, the pressure dropped to 90 mm. systolic and 60 mm. diastolic; and on standing to 60 mm. systolic with a diastolic level which could not be determined. With the change in blood pressure there was no remarkable change in pulse rate. The ability to perspire was apparently normal. Repeated examinations revealed the same findings.

The patient was placed on ephedrine, 25 mg. four times a day, with no apparent effect until one week had passed, when gradual continuous improvement started.

In general, in the precardiac variety pallor is a prominent finding. Characteristically in such episodes the patient is sitting or standing. Premonitory symptoms usually usher in the attack. The patient may fall heavily or gradually slip into the recumbent position. Emptiness in the epigastrium and nausea may develop before consciousness is lost. Both blood pressure and pulse fall, the first from vasodilatation, the second from vagal stimulation. Later the pulse may become rapid, unlike the pulse findings in the above case report. Facial pallor appears. Bursts of sweating develop. With unconsciousness the pupils dilate and the body becomes flaccid. Respirations are slow and deep.

This is the most frequent type of fainting and most commonly results from disturbances which are not serious, disturbances which brand syncope as a symptom usually of little importance as far as organic disease is concerned. Here, besides the fainting of postural hypotension, exemplified by Case 1, syncope associated with infections, stuffy environment, fasting, emotional distress, severe pain, and the like, must be placed. Further discussion of the general classification of syncope may be found in a recent report.[22] Syncope associated with serious disease, either vascular or nonvascular, may also fall into this group. Hemorrhage, shock pictures associated with coronary thrombosis or other disease, pain of renal or other varieties of colic, are such examples. The peripheral type of hyperactive carotid sinus reflex also falls into this group. This will be discussed further below.

These attacks usually last several minutes but may last up to 30 minutes and the patient may not develop his feeling of wellbeing for several hours. There is no particular relationship to effort or exertion, which, except in hemorrhage, would tend to encourage venous return. In postural hypotension the episodes may be repeated by changing the patient's position and confirmed by recording of blood pressure levels with the patient lying, sitting, and standing. The entrance of the carotid sinus into the episode may be tested by digital pressure over the sinus.

Syncope related to peripheral shock with serious disease is exemplified in the patients with coronary thrombosis recently reported by Cookson.[2] He found among 200 patients with acute cardiac infarction syncopal or epileptiform attacks in 15. Syncope occurred in 10 at the onset in the presence of apparently severe peripheral circulatory failure. In some, and particularly

those with syncope in the course of the infarction, abnormal rhythms were noted. In coronary occlusion it must also be noted that in certain instances arteriosclerotic disease probably has already impaired to some degree the cerebral circulation. In Cookson's 10 patients with syncope at the onset, five were 70 or more years old.

Syncope of the second type, resulting from impaired ability of the heart to pass on the blood presented to it is well known but not frequent in occurrence. The following case report exemplifies this group.

Case 2. S. S., a 44 year old housewife, complained of rapid heart action accompanied by episodes of vertigo, weakness and syncope. She had been suffering from these symptoms for several years with episodes occurring as frequently as three times a week. Their usual duration was about 10 to 20 minutes. Between the attacks she felt quite well and had no symptoms of any kind.

Physical examination disclosed little of importance. Blood pressure was 138 mm. Hg systolic and 80 mm. diastolic, pulse 80 per minute, respirations 18 per minute. Her fundi were normal. Thyroid was not palpable. Heart and lungs showed no remarkable findings.

Laboratory data were of no importance. The basal metabolic rate was + 6 per cent. Roentgenographic examination of the heart disclosed borderline figures with a transverse diameter of 14.3 cm. and the internal diameter of the chest 29.2 cm. Electrocardiograms obtained during the episodes showed evidences of a flutter mechanism with 2:1 ventricular response at a rate of 130, while at other times, particularly when vertigo and syncope were in evidence, tachycardia with a rate of 240 per minute in which one could not distinguish auricular flutter from paroxysmal tachycardia was present.

Treatment with digitalis and quinidine directed at the control of these symptoms was successful in markedly reducing the frequency of their occurrence.

Borg and Johnson [3] have discussed the differential diagnosis of syncopal attacks of this type. Two causes are given for the arrest in blood flow, one ventricular slowing or standstill, and the other ventricular tachycardia. In the former, cerebral blood flow is impaired by infrequency of ejections by the heart; in the latter, the rapid action of the heart makes it inefficient as a pump and cardiac output is markedly diminished. Coronary occlusion, especially of the right coronary artery, at times interferes with the circulation to the His bundle and produces some degree of heart block. Stokes-Adams syndrome occasionally develops in this way. Rapid ventricular tachycardia, 1:1 flutter, transient ventricular fibrillation, are examples of the second type. Comeau [4] believes that some episodes of syncope associated with auricular fibrillation arise on the basis of ventricular standstill with the onset of the mechanism rather than on the basis of the rapid mechanism itself.

The clinical picture of cardiac syncope differs from that of the precardiac type. The disturbances in rhythm already mentioned are found. Sweating is not an outstanding feature, but convulsions often are. When heart block is the cause, one may find some degree of heart block between attacks as well.

The postcardiac type implies a disturbed circulation somewhere between the left ventricle and the cerebrum. This picture varies and at times is

difficult to differentiate from epilepsy, as exemplified by Pal's crises and certain phases of hypertensive encephalopathic syncope, which fall into this group. Here too fall certain instances of syncope on exertion associated with heart disease.

Case 3. A. B., age 60, entered the hospital with complaint of ease of fatigue. History disclosed that on several occasions he had had loss of consciousness for a few moments while suddenly exerting himself.

Examination disclosed moderate generalized arteriosclerosis with no remarkable cardiac findings. The heart was not enlarged. There were no murmurs; the rhythm was regular; and the electrocardiogram was entirely normal. The eye grounds showed moderate arteriosclerosis.

Laboratory data, including blood count, Wassermann reaction and urinalysis, disclosed nothing abnormal. While ambulatory in the hospital the patient suddenly exerted himself in running down the hall and fainted. The episode lasted about five minutes, during which time blood pressure was normal, 124 mm. Hg systolic and 68 mm. diastolic; pulse was normal, 84 per minute; and respirations were 18 per minute. Electrocardiograms taken following this episode were similar to those taken before the attack and disclosed nothing abnormal.

Similar episodes were not repeated during the hospital stay and were not reproduced by digital carotid sinus stimulation.

Case 4. G. T., age 59, white male, was brought to the hospital complaining of precordial pain of 30 minutes' duration. The pain was described as heaviness in the retrosternal region and radiated to the left arm. The patient stated that with the onset of the pain he had fainted. Episodes similar to this had been present for several years, the first attack having occurred while he was plowing. Precordial pain developed, and in a few seconds syncope appeared. The patient recovered in what he estimated to be about 10 minutes and continued with his work. On several occasions since that time similar episodes had been experienced. On admission to the ward of the hospital the patient was free of pain. However, the next day he again experienced precordial pain associated with syncope which lasted about five minutes. During this time no electrocardiogram was taken, but the pulse was found to be regular and equal to the heart rate at a frequency of 80 per minute. Blood pressure was 130 mm. Hg systolic and 72 mm. diastolic and unchanged.

Further examination disclosed moderate peripheral arteriosclerosis with moderate arteriosclerotic changes in the eye grounds. Examination of the heart showed no enlargement. There was a soft, systolic aortic murmur which could be heard in the neck in expiration. The carotid sinus reflex was not hyperactive when tested.

Fluoroscopic examination of the heart disclosed no enlargement or dilatation of the aorta and no evidences of calcification of the aortic valve. There were no other remarkable findings. Electrocardiogram, temperature, sedimentation rate, and leukocyte count remained normal. In the absence of evidence of coronary occlusion the patient was discharged from the hospital with a diagnosis of angina pectoris and syncope on exertion.

As shown by these cases, the heart rate continued in the usual range. Blood pressure was not remarkably depressed and no particular change in color occurred. These findings clearly differentiate the syncope from both the precardiac and cardiac types. Although the relationship of syncope to cardiac manifestations is clear-cut in Case 4, in Case 3 no cardiac manifestations accompanied the attacks and coincidental disease, epilepsy, for

example, might be suggested. However, here also the relationship of syncope to exertion is definite, a finding which sets these pictures both aside as distinct and unusual entities. Whereas Cases 1 and 2 merely represent examples of those particular types of syncope, both Cases 3 and 4 deserve reporting because of their similarity to the unusual patients described by Gallavardin (*vide infra*).

Convulsive seizures may occur, an uncommon finding in the precardiac variety. This was not shown by our cases. Ferris et al.[5] found in a study of the carotid sinus reflex that the clinical manifestations of fits and syncope cannot be rigidly separated.

It is apparent that organic cardiac disease may be associated with syncope due to the precardiac, cardiac, or postcardiac mechanisms. Likewise, all three mechanisms may come into play in the absence of organic heart disease. This is exemplified by the carotid sinus syndrome in which three main types of cardiovascular reaction have been observed.[6] A marked fall in blood pressure may develop without remarkable cardiac slowing. Secondly, asystole, or sudden slowing of the pulse may account for the symptoms; and, thirdly, symptoms, including syncope, may be associated with paling followed by intense flushing of the face *without* slowing of the heart or a fall in blood pressure. This third group is an important one because there is no striking change in the general circulation, findings which brand the syncope as a postcardiac phenomenon. Weiss and Baker assume the fainting to be due to sudden changes in cerebral vessels from carotid sinus stimulation. The three types of carotid sinus syndrome exemplify the precardiac, cardiac, and postcardiac varieties of syncope. The terms, depressor, vagal, and cerebral, applied to the carotid sinus syndrome are not satisfactory in the general classification of syncope for the cardiac variety is not usually vagal in origin and the precardiac type may not be depressor.

Although the association of syncope with heart disease usually brings to mind the cardiac variety described above as associated with mechanismal disturbances, the association, in the absence of mechanismal disturbances, of syncope on exertion with heart disease has been given little attention in the literature. Congenital heart disease, particularly with hypoplasia of the aorta, aortic regurgitation and congestive heart failure, especially with pulmonary edema and cardiac asthma, are occasionally accompanied by syncope on exertion, but not as strikingly as angina pectoris and aortic stenosis. White [7] indicates that syncope is uncommon in angina pectoris but that in association with vertigo it occurs occasionally. He does not mention relationship to effort but this may be implied in angina pectoris. Chief interest is seen in the French literature where Gallavardin's reports have been stimulating. In 1922, he published a report [8] in which syncope was associated with auriculoventricular dissociation, but in 1928 [9] he also recorded a case in which there was a normal cardiac rhythm and aortic stenosis. More recently [10] he described two patients with syncope on effort.

In both instances evidences of aortic stenosis were present. Others have described similar cases [11, 12, 13] in which syncope produced by effort was an outstanding feature, and in each an aortic lesion was present. Associated anginal pain is described. Gravier's patient had a normal mechanism during the attacks. Halbron, Lenormand and Poncet found in their cases that auriculoventricular dissociation did not explain the syncope. Syncope lasted 15 to 20 minutes, too long for Stokes-Adams attacks and for ventricular standstill also. They, too, observed an unchanged pulse rate during an episode. In both our patients syncope was present when normal heart rates were present, although no confirming electrocardiograms were taken during the attacks. It appears that cardiac syncope does not explain these episodes, although one could postulate a failure of cardiac output to accompany the needs for blood on exercise.

The association with aortic stenosis of a train of symptoms including vertigo, weakness, precordial pain and, at times, sudden death, as well as syncope, is well known in the American literature, but little is said of the relationship of syncope to exertion. Willius,[14] in a study of 96 cases, found that 21 per cent had anginal pain. McGinn and White [15] found syncope in 22 per cent of their series and angina pectoris in 19. Also little is said of the association which exists between the cerebral manifestations and coronary pain.

The mechanism of these symptoms in this disorder has never been adequately worked out. Contratto and Levine,[16] in a study of postmortem material in 53 cases of aortic stenosis, found calcification limited to the aortic valve and not involving the coronary orifices. In two young patients the coronary arteries appeared normal and in other subjects there were minimal atheromata. They suggested that the deformity of the valve itself was in some way responsible for this complication, whereas others [17] believe it due to narrowing of the aortic valve. Autopsy material indicates clearly [16] in some of these individuals a pathologic process in the aortic valve not in close association with the coronary orifices. The aortic regurgitation often present does not seem responsible. LaPlace [18] found the degree of regurgitation, as judged by the diastolic pressure, showed no relationship to the occurrence of angina pectoris. Also angina pectoris occurs in aortic stenosis without regurgitation. Other explanations include a discrepancy between coronary circulation and cardiac work and the suction principle in which the abnormal aortic valves do not cover or protect the coronary ostia and presumably blood is allowed to be withdrawn from the coronary arteries.[16]

Marvin,[19] in his interesting report on this problem, concluded that syncope and other cerebral manifestations might be based upon activity of the carotid sinus. The reflex is often hyperactive in sclerotic subjects, particularly after digitalization. French reports [13] also favor some type of nervous mechanism. Observations already noted in the literature and confirmed in our patients indicate that the precardiac and cardiac types of reactions do not explain those instances in which a full regular pulse without

slowing was noted. The postcardiac, or so-called cerebral, type of carotid sinus reflex, in which a vascular disturbance rests upon stimulation of cerebral vessels independently from vagal slowing and the peripheral vascular effects, although the most uncommon type of reaction, can possibly explain these pictures. Weiss and Baker suggested anoxemia as a cause of fainting in the cerebral type. Ferris, Capps and Weiss have found changes in the spinal fluid dynamics associated with fainting following carotid sinus pressure which, to them, strongly suggested that variations in the caliber of the cerebral vessels frequently occur, but they showed evidence that the change in cerebral vessels is not the actual cause of fainting but merely a concomitant manifestation.[5] There are a number of facts which speak against the postcardiac type of carotid sinus mechanism entering into these pictures. In some of the reported cases syncope lasts longer than the one to three minutes described by Weiss et al.[20] In addition, with the cerebral type of carotid sinus reaction, no particular relationship to exertion has been found, a striking fact in ours as well as in the reported cases. Contratto and Levine, in 19 patients with aortic stenosis, found two with a clear-cut history of syncope but could find no positive results with carotid sinus pressure although they do report two patients without syncope but with both aortic stenosis and a definitely positive reaction to carotid sinus pressure. Furthermore, in our two patients digital stimulation of the carotid sinus produced no abnormal response.

As already stated, attempts to explain both the syncope and anginal pain have not been satisfactory. That both occur in aortic stenosis is so well known that one would suspect this diagnosis with their presence. This is also true when the syncope is related to exertion in the several instances reported in the literature. In both of our patients clinical means, including fluoroscopy, did not permit the establishment of the diagnosis of aortic stenosis, and, since both patients are still living, autopsy confirmation is not possible. The usual absence of syncope on exertion in simple coronary arteriosclerosis would lead one to believe that an additional factor, perhaps aortic narrowing, without adequate diagnostic criteria, was present. The fact remains that with or without aortic stenosis attempts to explain both syncope and anginal pain have not been fruitful. Severe pain, whether related to the heart or not, is known to be sufficient to excite the precardiac type of syncope. In the instances herein reported, as well as in some of those in the literature, precardiac syncope did not occur and also there has been no correlation between severity of pain and syncope. In fact, some of the patients developed syncope with little or no pain, as did our Case 3, and in some instances pain has not appeared until consciousness is regained. Severe anginal pain commonly occurs without syncope. Indeed, attempts to explain angina pectoris and syncope on the same grounds meet with difficulty. At times it has been reported that both syncope and angina may be relieved or prevented by nitroglycerine. Exertion to be sure may precipitate each. However, syncope often outlasts the time interval over which angina usually

lasts. Syncope lasting over half an hour has been described in some instances.[21] In Gupta's patient the occurrence of syncope of two hours' duration with pain on recovery of consciousness speaks against angina pectoris.

Our willingness to rule out cardiac and precardiac syncope as the types occurring in certain patients with angina pectoris or aortic stenosis certainly does not indicate that these types of syncope cannot and do not enter into the clinical picture in some instances. Nor does our evidence rule out the possibility that at times the carotid sinus reflex may play a part in these pictures, particularly as a cause of sudden death in some patients. However, in our patients and in several already referred to from the literature these mechanisms do not appear to be active.

Summary

Syncope may be classified into three types, depending upon the mechanism of its production. For a general clinical classification the terms, precardiac, cardiac and postcardiac, have been suggested. The clinical manifestations usually permit recognition of the mechanism involved, a satisfactory classification of the patient, and lead to a more rational approach to therapy.

The relationship of syncope on exertion to cardiac disease has been emphasized and two case reports illustrating this unusual manifestation are added to the several in the literature. The diagnostic value of syncope on exertion is pointed out.

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CALCIFIC AORTIC VALVE STENOSIS: A CLINICO-PATHOLOGIC CORRELATION OF 22 CASES*

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THE importance of calcific aortic valve stenosis is manifest when one considers that it occurs in any age group, produces symptoms which are not common to other valvular lesions and may result in sudden death without previous cardiac decompensation. Too frequently the lesion at autopsy has been entirely unsuspected. Symptoms of cardiac disease may be absent despite marked valvular stenosis and postmortem evidences of valvular disease of long duration.

This condition has been known to pathologists as calcareous or calcified aortic valve stenosis, calcific sclerosis of the aortic valve, atherosclerotic calcification of the aortic valve, calcific nodular valvular sclerosis, Mönckeberg's annular or aortic sclerosis and primary ascending sclerosis of the aortic valve. Although accurately described by Mönckeberg [1] as far back as 1904, its only interest was as an occasional postmortem finding.

It is hoped that this study, through the close correlation between clinical and pathological material, may shed some light on the diagnosis of this lesion, its genesis and insidious development, and the reasons for the failure to recognize it during the life of the patient.

MATERIAL FOR STUDY

Twenty-two autopsied cases of pure calcific aortic valve stenosis were available for study. This represented a consecutive series of cases found at the autopsy table at Kings County Hospital from 1934 to 1942. They were carefully selected on the basis of calcareous infiltration of the aortic valve leaflets only, in the absence of significant degrees of involvement of other valves. The very occasional occurrence of very small atheromatous plaques or thickening of the mitral valve leaflets was disregarded since they were minimal and occurred not more frequently, nor to any greater degree than was observed in apparently normal hearts of persons of corresponding ages. Cases with other valvular defects were carefully avoided so that only the effects of a pure aortic stenosis on the size and weight of the heart, symptomatology, physical findings, electrocardiogram and on the production of other confusing murmurs could more clearly be defined and evaluated.

Clinical Diagnosis. Diagnostic criteria consist of the history, characteristic pulse, palpable thrill over the base of the heart, loud rough systolic murmur at the base of the heart or entire precordium heard loudest over the aortic valve, decreased intensity or absence of the second aortic sound and cardiac

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hypertrophy. Visualization by fluoroscopy, occasional demonstration on the roentgenogram and electrocardiographic changes are helpful laboratory aids.

Symptoms

1. Symptoms of Left Ventricular Failure. These are usually the first evidence that the patient is suffering from heart disease. They are exertional dyspnea, paroxysmal nocturnal dyspnea and orthopnea. In our series they occurred 17 times (77.3 per cent). This may be followed by the usual signs of right ventricular failure. Varying degrees of ankle swelling were mentioned 11 times (50 per cent).

2. Angina Pectoris. Precordial pain was reported nine times (40.9 per cent). It occurred despite normal or only slightly diseased coronary arteries. Such pain rarely occurs with mitral stenosis or aortic insufficiency unless the coronary ostia are damaged. Precordial pain is a frequent accompaniment of aortic valve stenosis, but is sometimes caused by coronary sclerosis. Some attribute it to a concomitant aortic insufficiency. Contratto [21] and Levine [8] are of the opinion that the pain is due to myocardial ischemia caused by suction of blood from the coronary arteries by the accelerated blood flow.

3. Dizziness. This symptom was noted seven times (31.9 per cent). Dizziness is due to a transient cerebral anemia caused by an insufficient aortic output. In some instances it may be due to hyperactive carotid sinus reflex or both factors may be involved.

4. Syncope. Attacks of syncope were noted only once (4.6 per cent). It is possible that a larger percentage could have been elicited with more thorough interrogation. The explanation for these attacks is similar to that of the dizziness.

Physical Findings

1. Systolic Aortic Murmur. A systolic murmur that is confined to the aortic area is almost without exception indicative of disease of the aorta or aortic valves, namely, aortic stenosis, aortic sclerosis or aortitis, whereas a systolic murmur that is audible in the pulmonary area is of little significance. This fact is important since Willius [15] found that many patients who presented an aortic systolic murmur were accepted for active service during the first World War, but on examination 15 to 20 years later all exhibited well-marked calcareous stenosis of the aortic valve. The murmur may be heard over the entire precordium and is transmitted to the neck, but it is loudest over the aortic area. The presence of such a murmur was discovered in only 16 cases of the present series (72.8 per cent). However, though the murmur was present, the diagnosis of an aortic stenosis was not made in five of these cases (31.3 per cent). Among possible reasons for this error were the misinterpretation of the murmur, the confusion due to the presence of other murmurs, and the absence of corroborative findings such as systolic thrill or absence of the second aortic sound.

2. Aortic Thrill. This was present only six times in all the cases (27.3 per cent). Its occurrence in the 16 patients who had an aortic systolic murmur was only 37.5 per cent. The best way to palpate the thrill is to place the palm over the aortic valve with the patient leaning forward slightly during full exhalation.

3. Other Murmurs. The presence of other murmurs was noted 16 times (72.8 per cent). In view of the fact that our pathologic material was carefully selected for absence of other valvular involvement, reasons were sought for their occurrence and especially because of confusion in the clinical diagnosis and evaluation.

It was not uncommon to find an associated soft, low-pitched murmur of aortic regurgitation. Like the aortic systolic murmur and thrill, it is more easily heard following exercise, while leaning forward and during expiration. Despite the presence of a diastolic murmur in nine of our cases (40.9 per cent), there was no dynamically significant insufficiency and the peripheral phenomena of aortic regurgitation were almost always absent. Two of these cases had positive Wassermann reactions and presented signs clinically suggestive of an insufficiency, but the pulse pressure was small.

Apical murmurs were heard in 16 cases (72.8 per cent) despite normal mitral valves. They were variously described as soft, loud or rough. The presence of a systolic murmur at the apex has two possible explanations. Either the maximum intensity of the murmur of aortic stenosis was mistakenly placed at the apex or a relative mitral insufficiency was present due to dilation of the left ventricular chamber (cases 1 to 7 inclusive, 9 to 13 inclusive, 15 and 22). A presystolic apical murmur may be explained on the basis of an Austin-Flint murmur due to aortic regurgitation (cases 6, 7 and 11). A diastolic murmur at the apex may be due to transmission from an insufficient aortic valve (cases 5, 10, 16, 20, 22).

4. Second Aortic Sound. Although it is usually described as absent or diminished with increasing stenosis, it was found to be completely absent only twice in our series (9.1 per cent). Varying degrees of diminution of intensity were not noted.

5. Blood Pressure. The blood pressure usually reflects the palpatory characteristics of the pulse. Unless there is a concomitant hypertension the systolic pressure is not elevated or only slightly so, or it may be lowered. Diastolic pressures are decreased or normal, resulting in a pulse pressure that is often normal or decreased. However, when the aortic regurgitant factor is present and marked in degree the pulse pressure may be increased.

In our series, the highest systolic pressure (with one exception of 220 mm.) was 174 mm. and the lowest was 90 mm., with an average of 140 mm. of mercury. The diastolic pressures ranged from 30 to 120 with an average of 77 mm. of mercury. The average pulse pressure was 63 mm. of mercury. The higher pulse pressures were due to the frequent presence of a concomitant hypertension and aortic regurgitation.

6. The Pulse. The radial pulse of aortic stenosis is classically described as "rarus, parvus, tardus et longus." There is a definite halt in the rise of pressure in the radial pulse as determined by the radial sphygmogram or expert palpation in severe cases. This causes the principal peak to occur later in the cycle than normally. Recently, Dow [22] has shown experimentally that stenosis so reduces the violence of the systolic discharge that standing waves are not set up and the peripheral pulse reproduces the central pulse form with almost complete faithfulness. The stenosis offers so much resistance to flow during mid-systole that the central pulse itself assumes the anacrotic and tardus characteristics.

The pulses in our series were variously described as: regular but weak, fair quality or volume, poor volume, rapid and small, and in three cases with regurgitant factors of the Corrigan type. The classical description was not noted in our series. However, it must be remembered that other factors may have influenced the plateau pulse. These were age, hypertension, arteriosclerosis and aortic insufficiency. Even sclerotic changes in the radial artery made detection difficult.

Laboratory Aids

1. Roentgenographic and Fluoroscopic Examination. The roentgenographic and fluoroscopic diagnosis of calcium deposits in the valve leaflets by special technic has been amply described.[23] In 36.4 per cent of our series (approximately the figures of Dry and Willius [16] — 35 per cent) diagnosis based on history and physical findings was confirmed by autopsy. They have demonstrated that the frequency of identification may be almost doubled (64 per cent) by the additional fluoroscopic demonstration of calcification of the aortic leaflets or annulus. Arteriosclerotic dilation of the aorta may be differentiated by roentgenographic demonstration of the dilatation and calcific plaques in the aorta rather than calcification in the region of the valve.

2. Electrocardiography.[16, 24, 25] Left ventricular strain was evidenced by left axis deviation and T-wave negativity in Lead I or Leads I and II. The presence of this additional T-wave negativity (also may be diphasic) is proof of greater left ventricular strain than left axis deviation alone. This is important, since in cases in which aortic stenosis exists alone the stress is borne principally by the left ventricle. In aortic insufficiency hypertrophy of all the cardiac chambers may ensue. When mitral stenosis and other lesions exerting strain on the right ventricle coexist, this chamber hypertrophies and both sides of the heart participate in varying degrees in sharing the abnormal strain. Hence, when right ventricular strain exists other valve involvement, pulmonary artery atherosclerosis, overdigitalization, or infarctions (producing T-wave depression) must be looked for.

Electrocardiographic studies made in 10 cases of our series showed a left axis deviation in all but two of the cases (80 per cent). The T-wave in

Lead I was isoelectric, negative or diphasic in all but one case. Another case with rheumatic etiology presented both complete heart block and left bundle branch block. Auricular fibrillation and pulsus bigeminus occurred once each. The heart rates ranged from 40 to 115 with an average rate of 91 per minute.

Pathologic Lesions of Aortic Valve

The lesion of calcific aortic valve stenosis is characterized by a tendency to hyalinization of the connective tissue, depositions of lipoid material in the aortic valve ring and in the aortic valve and subsequent calcification of the affected tissues. Clawson et al.[4] found calcium by gross examination in 84 per cent of all non-syphilitic deformities of the aortic valve. Willius and Dry [14] found no instance of stenosis unassociated with some calcium deposit. Detailed histopathologic investigations by Sohval and Gross [13] offer evidence that a primary degenerative disease of the valve may be differentiated from those caused by rheumatic fever. Essentially, calcification in the former begins at the base of the valve and affects the fibrous portion of the valve on the aortic surface, whereas the latter occurs in the distal third involving the spongiosa and ventricularis layers on the ventricular aspect of the aortic cusps.

In addition, they demonstrated that healed rheumatic deformities could be found in various significant sites, i.e., left auricle, valve rings and valve cusps, pericardium and several valves may be affected. The degree of calcification closely parallels the degree of stenosis, but sclerosis of the aorta and coronary vessels is likely to occur in inverse proportion to the degree of stenosis of the aortic valve. Paralleling Cabot's early collection of autopsied cases,[7] a terminal acute endocarditis was superimposed on the calcified lesion three times, twice in cases of chronic rheumatic valvulitis (cases 7 and 16) and once in a patient with arteriosclerosis (case 3).

The gross lesions of the aortic valve can be characterized in one of the following ways:

1. Calcific nodules of varying sizes occur in the substance and base of the valve rather than in the free margins, thus producing a thickening of the valve. Marked deformities and stenosis result in the advanced group which may make a differentiation between a true and false bicuspid valve difficult.
2. Calcific deposits and ridges are often found in the sinuses of Valsalva. The aorta frequently remains free from atheromatous changes.
3. Calcific deposits may assume ragged, rounded or ridge-like shapes and may ulcerate through the endocardium with superimposed thrombus formation, especially in the terminal phase.

Etiology

Although considerable controversy is still prevalent concerning the existence of certain lesser factors in the causation of calcific aortic valve steno-

sis, rheumatic fever and arteriosclerosis have a definitely established relationship to the condition (table 1).

1. Rheumatic Fever. That calcareous stenosis might be of a rheumatic nature was first suggested by Christian.[2] This view was upheld by the studies of Dry and Willius [3] and Clawson, Noble and Lufkin,[4] who believed it to be the only factor involved. This was based upon a history of rheumatic fever, old healed defects of other valves, and the relics of pericarditis. These opinions have been further corroborated by Friedberg and Sohval [5] and especially by the excellent microscopic studies of Karsner and Koletsky.[6] The latter found some evidence of rheumatic fever in 37 out of 40 cases

TABLE I
Sex and Etiological Distribution

	Male	Female	Total
Arteriosclerosis	14	2	16
Rheumatic fever	4	1	5
Subacute bacterial endocarditis	—	1	1
Total	18	4	22

under study. They felt that if the Mönckeberg type of aortic valvular sclerosis existed, it could not be distinguished morphologically from that associated with chronic or healed rheumatic fever. Delafield and Prudden [12] stated that among the most common and important examples of calcareous degeneration may be mentioned those which occur in the heart valves in endocarditis. From a clinicopathological study of 28 cases of pure aortic disease, Cabot [7] also concluded that it was due to a rheumatic endocardial infection. A history of rheumatic fever could not be elicited in more than 22 per cent of the cases.[3] The remainder suffered very mild or atypical episodes which went unrecognized. Clawson et al.[4] obtained a history of rheumatic fever in 35 per cent of their series.

Since our case studies were based on selected material with exclusion of associated valvular defects, it must be realized that statistically the avoidance of patients with more frequent involvement of other valves markedly depreciated the frequency of rheumatic fever as an etiological factor. Most of our cases were specifically questioned concerning rheumatic episodes, and this was present in three out of five cases (60 per cent). An even greater percentage probably was not found because the infection was so mild or atypical that its true nature went unrecognized. Yet, it is important to note that our cases were drawn from the Middle Atlantic States where rheumatic infections are severe. The total number of cases considered to be of rheumatic origin, from history as well as pathologic findings, was only five out of 22 cases (22.3 per cent).

2. Arteriosclerosis. Although atherosclerotic calcification of the valve was originally considered as the factor of prime importance, there has been

a tendency of late to abandon this view. The objection raised to the possibility of a primary degenerative disease of the valve is that the aorta showed less or even no calcification. This is not valid, since it cannot be argued that atherosclerosis of the aorta is not degenerative because the valve is not affected. According to White,[9] both calcification secondary to rheumatic or other types of infectious endocarditis and primary atherosclerotic degeneration may exist together.

In our series, an arteriosclerotic factor occurred in 16 cases (72.7 per cent). No history of rheumatic fever or stigmata of rheumatic disease were revealed at autopsy in any of the cases. A past history could not be ascertained in two cases due to deaf mutism and unconsciousness. Therefore, when the aortic valve alone is involved, the arteriosclerotic factor is much more important than the rheumatic (large table). However, this probably does not hold true when other evidences of rheumatic involvement are present (mitral valve disease, pericardial disease or disease of the endocardium).

3. Subacute Bacterial Endocarditis. The supposition that subacute bacterial endocarditis is an underlying factor has been supported by Libman,[10] Perry,[11] and others. They are of the opinion that calcification may occur as part of the healing process in subacute bacterial endocarditis after the patient becomes bacteria free. Subsequently, after months or years, there may be a reinfection of the diseased valve, usually by the *Streptococcus viridans.*

We found one such case (case 17) in our series (4.6 per cent) occurring in a 41 year old female with a cardiac history of eight years' duration. It might be argued that the subacute vegetations were superimposed on atheromatous ulcerations, rather than a healing and calcification end stage of primary subacute bacterial endocarditis. The age group in which such cases occur, however, probably precluded a primary atherosclerosis of the valve with a superimposed infection. It was difficult to state with any degree of certainty whether the calcification followed the initial rheumatic involvement or the bacterial invasion. In answer to those who consider this factor inoperative, it may be stated that since healing has been repeatedly reported in such cases, there is no reason why it should not terminate in calcification as an end result.

4. Syphilis. In three of our cases (6, 10, 22), a four plus Wassermann reaction and syphilitic aortitis were demonstrable at postmortem examination (13.7 per cent). Two of these cases also showed rheumatic lesions and one arteriosclerosis. In the Sohval and Gross [13] series of 15 cases, there was concomitant aortitis and aortic insufficiency in four cases. According to White,[9] aortic stenosis is not the result primarily of syphilis, although infrequently in healed cases calcification or subacute bacterial endocarditis may be found as a complication causing some degree of stenosis. Christian [2] is of the opinion that syphilis definitely plays no part in the etiology even

History

No.	Patient	Age	Sex	Past History	Dizziness	Angina	Syncope	Other Symptoms
1	C. P.	62	M	Negative	–	–	–	Dyspnea. Edema
2	L. L.	55	M	Found unconscious				
3	T. L.	70	M	Deaf mute				Dyspnea
4	E. S.	75	M	Negative	+			Edema. Dyspnea. Orthopnea
5	S. J.	82	F	Negative	+			Edema. Dyspnea
6	N. J.	25	M	Rheumatism at 9 yrs.	+	++++		Edema. Dyspnea
7	W. B.	52	M	Rheumatic polyarthritis at 40 yrs. with heart involvement		++++		Dyspnea. Cyanosis
8	W. L.	54	M	No past history. Onset present illness with pneumonia	–	–	–	
9	H. W.	55	M	No rheumatic history		–		Paroxysmal nocturnal dyspnea
10	H. R.	58	M	No rheumatic history	+	–		Edema. Dyspnea. Orthopnea
11	J. A.	36	M	No rheumatic history; passed insurance exam. 9 years ago				Edema. Dyspnea
12	L. E.	59	M	Negative		+		Edema
13	V. D.	71	M	Previous attack of cardiac decompensation	+	++		Dyspnea. Edema
14	P. G.	80	M	No rheumatic history		–		Dyspnea. Edema
15	R. W.	61	M	No rheumatic history	++		++	Dyspnea
16	G. K.	35	F	Rheumatic heart trouble since childhood	++	++++		Dyspnea. Edema
17	F. C.	41	F	Cardiac for 8 yrs.		+++		Dyspnea
18	E. S.	57	F	No cardiac history. Admitted for common duct stones.	–	–		
19	C. B.	62	M	No rheumatic history		++++		Edema. Paroxysmal nocturnal dyspnea
20	M. M.	72	M	Negative		++		Edema. Dyspnea
21	L. S.	77	M	Negative		–		Edema
22	S. C.	43	M	No rheumatic history		++++		Dyspnea

Physical Findings

No.	Patient	Age	Sex	Aortic Systolic	Aortic Thrill	Aortic Dias.	Other Murmurs	A_2	B. P.		Pulse		Cardiac Hypertrophy	Rhythm	E K G	Clinical Diagnosis	Diagnosis Correct	Duration Cardiac Illness	Duration Hospital Stay
									Sys.	Dias.	Type	Rate							
1	C. P.	62	M	++++			Rough systolic at apex and base, loudest at base		130	100	Fair volume	110	+++	RSR		Arteriosclerotic heart disease with decompensation	No	6 mos.	1 day
2	L. L.	55	M				Systolic at apex		160	120	Poor volume	76	–	RSR		Cerebral hemorrhage	No	?	1 day
3	T. L.	70	M	++++		–	Systolic at apex and base	Absent	132	70	Fair quality	84	++	RSR		Aortic valve sclerosis	Yes	4 yrs.	4 yrs.
4	E. S.	75	M	++			Systolic at apex and 3rd left intercostal space		174	106	?	?	++++	RSR		Chr. myocarditis; gen. arteriosclerosis	No	6 mos.	1 day
5	S. J.	82	F			+	Blowing systolic and diastolic at apex		220	110	Fair volume	75	++	AF		Arteriosclerotic heart disease; gen. arteriosclerosis	No	1 yr.	5 days
6	N. J.	25	M	++	++	++	Systolic and presystolic at apex. Duroziez		150	110	Corrigan	100	++++	RSR	No axis deviation; sinus tachycardia	Rheumatic and luetic heart disease (++++ Wass.)	Yes	3 mos.	2 mos.
7	W. B.	52	M	++	++++	+	Systolic and presystolic at apex		110	60	Corrigan	90	++++	RSR		Rheumatic heart disease	Yes	4 yrs.	2 mos.
8	W. L.	54	M				None		92	60	Rapid, irregular, fair quality	90	–	AF	Left axis deviation; auricular fibrillation; myocardial fibrosis	No cardiac diagnosis; lobar pneumonia	No	3 days	9 days
9	H. W.	55	M	+++	+++	+	Rough systolic at apex		148	70	Fair volume	110	+++	RSR	Left axis deviation; myocardial fibrosis	Chr. rheumatic valvular heart disease	Yes	6 mos.	2 wks.
10	H. R.	58	M	++++		+	To and fro at apex; heard best at base		130	65	Weak	90	++++	RSR	Left axis deviation; myocardial fibrosis; pulsus bigeminus at times (160)	Luetic heart disease. (++++ Wass.)	No	5 yrs.	1 mo.
11	J. A.	36	M	++++		++	Austin-Flint		150	30	Fair quality	90	+++	RSR	Left axis deviation; myocardial damage	Luetic heart disease. (++++ Wass.)	No	3 mos.	2 mos.

Physical Findings

No.	Patient	Age	Sex	Aortic Systolic	Aortic Thrill	Aortic Dias.	Other Murmurs	A2	B. P.		Pulse		Cardiac Hypertrophy	Rhythm	E K G	Clinical Diagnosis	Diagnosis Correct	Duration Cardiac Illness	Duration Hospital Stay
									Sys.	Dias.	Type	Rate							
12	L. E.	59	M	++			Systolic at apex		150	80	Fair quality	100	+++	RSR	Left axis deviation	Arteriosclerotic heart disease	No	13 days	10 days
13	V. D.	71	M	++++	++	−	Soft systolic at apex		162	70	Fair volume	70	++	RSR		Arteriosclerotic heart disease with aortic stenosis	Yes	1 yr.	17 days
14	P. G.	80	M	++			None		170	70	Fair volume	95	?	RSR		Hypertensive heart disease with acute myocardial failure	No	5 wks.	1 day
15	R. W.	61	M	−	−		Systolic at apex		160	100	?	40	++	Complete heart block	Left axis deviation; complete heart block; left bundle branch block	Stokes-Adams syndrome	No	8 mos.	2 wks.
16	G. K.	36	F	+++	−		Double murmur at apex		110	68	Rapid and small	120	++	RSR	Left axis deviation	Chr. rheumatic heart disease	Yes	1 yr.	1 wk.
17	F. C.	41	F	++	−		None		136	90	Weak	110	++	RSR		Subacute bacterial endocarditis	Yes	8 yrs.	3 days
18	E. S.	57	F	−	−	−	None		135	90	?	80	+	RSR		Acute toxic hepatitis, secondary to stones	No	11 days	11 days
19	C.B.	62	M	−		−	None		90	65	Weak	115	−	RSR	No axis deviation; myocardial damage; sinus tachycardia	Arteriosclerotic heart disease with decompensation	No	6 yrs.	1 day
20	M. M.	72	M	+++		+++	Diastolic at apex		168	60	Corrigan	90	+++	RSR x-systoles		Hypertensive heart disease with possible luetic aortic insufficiency	No	6 wks.	2 days
21	L. S.	77	M	++++	+++	−	None	Absent	110	60	Poor volume	100	+	RSR		Arteriosclerotic heart disease with calcific aortic stenosis	Yes	Few yrs.	1 wk.
22	S. C.	43	M	++++	++	++	Double murmur at apex		110	70	?	100	+++	RSR	Left axis deviation; severe myocardial damage	Luetic aortitis; coronary insufficiency (++++ Wass.)	No	4 wks.	13 days

Pathology

No.	Patient	Age	Sex	Description of Aortic Valve	Etiology Valve Disease	Heart Weight in Grams	Cause of Death
1	C. P.	62	M	Fused into 2 very stiffened and calcified cusps with large nodular calcified masses attached to each of the cusps. The orifice is a very narrow slit.	Arteriosclerosis	650	Pulmonary edema
2	L. L.	55	M	Many calcific, yellow-white nodules along cusps with a stenosis admitting a lead pencil.	Arteriosclerosis	550	Cerebral hemorrhage; bronchopneumonia
3	T. L.	70	M	Fresh fibrinous vegetations of the posterior and right anterior cusps involving both surfaces, superimposed on markedly sclerotic calcified process with immobility and marked stenosis. Acute vegetative endocarditis superimposed on chronic calcified aortic valve leaflets.	Arteriosclerosis	580	Myocardial insufficiency; uremia
4	E. S.	75	M	Marked stenosis of the buttonhole type. Leaflets markedly inelastic and covered with many calcific nodules.	Arteriosclerosis	Much enlarged heart, cor bovinum type. No weight stated	Chr. myocarditis; bronchopneumonia
5	S. J.	82	F	Cusps are thickened and calcified with rolled edges. The commissures are moderately fused preventing proper opening of valve.	Arteriosclerosis	400	Thrombosis sup. mesenteric artery; hypernephroma
6	N. J.	25	M	Marked thickening and hardening of valve leaflets with stenosis. Luetic aortitis present but not involving valve. No evidence of rheumatic fever.	Rhematic fever	520	Chr. myocarditis; bronchopneumonia
7	W. B.	52	M	Valve is greatly shrunken and sclerotic with many fine calcified irregularities on the ventricular surface. Five mm. ulceration present. Stenosis is marked, with marked fusion and calcification. Acute endocarditis of valve superimposed on healed rheumatic endocarditis.	Rheumatic fever	960	Adenocarcinoma of stomach
8	W. L.	54	M	Marked stenosis and calcification with extreme rigidity. Aorta is negative.	Arteriosclerosis	280	Lobar pneumonia
9	H. W.	55	M	Aortic valve is calcified and of buttonhole stenotic type. The edges of the cusps are very thick, calcified and curl upward.	Arteriosclerosis	720	Bronchopneumonia
10	H. R.	58	M	Marked stenosis and calcification with fusion of 2 leaflets. Luetic aortitis not involving valve.	Arteriosclerosis	850	Pulmonary edema
11	J. A.	36	M	Cusps are markedly thickened and hardened and stenosed with edges rolled back and distorted. Acute and chronic rheumatic valvulitis.	Rheumatic fever	700	Acute and chronic rheumatic endocarditis

Pathology

No.	Patient	Age	Sex	Description of Aortic Valve	Etiology Valve Disease	Heart Weight in Grams	Cause of Death
12	L. E.	59	M	Not described fully other than marked aortic stenosis and thickening.	Arteriosclerosis	410	Bronchopneumonia
13	V. D.	71	M	Cusps are all thickened, nodular and calcified. The opening is contracted to 5.5 cm. and the cusps so cartilaginous as to be immovable.	Arteriosclerosis	610	Generalized arteriosclerosis
14	P. G.	80	M	Valves are markedly sclerotic and inflexible. The commissures are fused, producing a calcific stenotic lesion.	Arteriosclerosis	500	Pulmonary edema
15	R. W.	61	M	Cusps are fused, thickened and calcified, resulting in stenosis due to old rheumatic fever.	Rheumatic fever	420	Pulmonary edema
16	G. K.	36	F	Valve is markedly distorted, calcified and stenosed with superimposed friable fine vegetations. Large ulceration at base of semilunar valve. Acute verrucous endocarditis superimposed on chronic rheumatic endocarditis with marked calcific aortic stenosis.	Rheumatic fever	600	Pulmonary infarction
17	F. C.	41	F	Aortic valve is markedly stenosed, hardened and distorted with ulcerations at edges of cusps. Subacute ulcerative endocarditis with calcific stenosis of aortic valve and multiple embolization.	Subacute bacterial endocarditis	500	Left ventricular failure with multiple embolization
18	E. S.	57	F	Valve is involved by marked arteriosclerotic calcification, especially at commissures with narrowing of lumen.	Arteriosclerosis	470	Acute toxic hepatitis secondary to stones
19	C. B.	62	M	Valve is markedly thickened and calcified with fishmouth orifice. Only 2 cusps are distinguished with calcified nodules throughout the valve.	Arteriosclerosis	540	Pulmonary infarction
20	M. M.	72	M	Valve presents thickening, hardening and fusion at the commissures. No evidence of lues.	Arteriosclerosis	Markedly enlarged. No weight stated	Bronchopneumonia
21	L. S.	77	M	Valve is markedly thickened, calcified, stenosed, with irregular yellow-white nodules.	Arteriosclerosis	580	Bronchopneumonia
22	S. C.	43	M	The anterior cusps are solidly fused. The posterior cusp is ulcerated at its free edge with superimposed fresh thrombi. Valves are markedly calcific, nodular and ulcerated. The calcific nodules are more prevalent at the base of the aortic surface of the valve. There is luetic aortitis not involving the valve.	Arteriosclerosis	670	Pulmonary edema

when there is a positive Wassermann reaction and syphilitic aortitis. He insists that syphilitic valvulitis with stenosis of the valves does not occur and only a regurgitant lesion can be produced by syphilis. Hence, the finding of syphilitic stigmata should be regarded as a concomitant lesion.

5. Miscellaneous Factors. Other conditions have been implicated from time to time.[3, 14, 15, 16] The facts and evidence in their favor have been so meager as to fail to establish them as acceptable factors. They require only the briefest mention.

(*a*) Cases of congenital aortic atresia have been reported in the literature in which the three leaflets persist as rudimentary ridge-like structures which are fused.[17] It usually occurs in association with a septal defect and may become calcified.

(*b*) Calcification of a bicuspid aortic valve.

(*c*) General toxic, distant infectious processes,[18] or an unidentified form of chronic inflammation.

(*d*) Proof is wanting for a metabolic cause of the disease.[19]

Age and Sex Distribution

The greatest number of cases occurred in the age groups of 50 to 80 years. The ages ranged from 25 to 82 years with an average age of 59 years. As was to be expected, a rheumatic etiology was most marked in the younger age groups (25, 36, 36, 52 and 61 years of age respectively with an average age of 42 years). The arteriosclerotic group was composed of the following ages: 43, 54, 55, 55, 57, 58, 59, 62, 62, 70, 71, 72, 75, 77, 80 and 82 years, with an average age of 65 years.

Table II

Age-Sex Distribution

Age Groups	Male	Female	Total
10–19	0	0	0
20–29	1	0	1
30–39	1	1	2
40–49	1	1	2
50–59	6	1	7
60–69	3	0	3
70–79	5	0	5
80–89	1	1	2
Total	18	4	22

The incidence of males was slightly more than four times that of females for the entire series (tables 1 and 2). These statistics are similar to those of Margolis et al.[20] and Contratto.[21] Males were involved to a far greater extent in the arteriosclerotic group, but in the rheumatic group both sexes were equally attacked.

Cardiac Enlargement and Heart Weights

Hypertrophy of the heart was due to a combination of several factors. These consisted of the mechanical obstruction of stenosis (with or without relative insufficiency) and hypertension. The reason why there were so many of these large hearts with unimpaired cardiac reserve is that the development of the cardiac hypertrophy proceeded subtly and the coronary flow remained adequate. The heart tolerates stenosis of the aortic valve far better than a mitral stenosis. Indeed, a tremendous heart may be an unexpected finding at autopsy examination.

Without corrections for obesity and hypertension, the heart weights ranged from 400 grams (with one exception of 280 grams) to 960 grams, with an average of 575 grams (table 3). This quite accurately paralleled the degree of enlargement found clinically.

Table III

Heart Weights (in grams)

200–299	300–399	400–499	500–599	600–699	700–799	800–899	900–999
280	—	400	550	650	720	850	960
		410	580	610	700		
		420	520	600			
		470	500	670			
			500				
			540				
			580				

Duration of Cardiac Illness

Following the onset of the first symptoms, the total duration of the illness ranged from three days to eight years (large table). It proved to be variable in all etiologic, age and sex groups. The hospital stay was more uniform and much shorter, ranging from one day to two months, with one exception of four years. The rheumatic group had a tendency to a longer hospitalization period than the arteriosclerotic group.

Causes of Death

The course was generally slow and progressive, the valve becoming more and more stenosed as more calcium was deposited on the leaflets. Therefore, it was present for many years even without cardiac symptoms, but when congestive failure finally ensued the duration of life was short. Auricular fibrillation occurred in 14 per cent of Dry and Willius' cases,[25] but it must be emphasized that half of these were complicated by the involvement of other valves. Auricular fibrillation was rare when there was a left axis deviation. Solitary aortic stenosis is tolerated by the heart much better than mitral stenosis alone.

Extracardiovascular causes of death (table 4) occurred in nine cases (40.9 per cent). Of the cardiovascular causes (table 4) pulmonary edema and congestive heart failure accounted for eight cases (36.4 per cent). Vascular accidents and disease accounted for five deaths, 20.8 per cent (1 generalized arteriosclerosis, 2 pulmonary infarctions, 1 cerebral hemorrhage, and 1 thrombosis of the superior mesenteric artery). These figures are similar to those of other authors.

TABLE IV

Cause of Death	No. of Cases
Bronchopneumonia	6
Pulmonary edema	5
Congestive heart failure	2
Pulmonary infarction	2
Acute rheumatic carditis	1
Thrombosis superior mesenteric artery	1
Cerebral hemorrhage	1
Generalized arteriosclerosis	1
Lobar pneumonia	1
Adenocarcinoma of stomach	1
Acute toxic hepatitis	1
Total	22

The possibility of sudden death existed in five cases, all of arteriosclerotic origin, who were acutely ill for less than 24 hours. One could not say with complete assurance that these cases were sudden deaths rather than acute myocardial failure or massive pulmonary infarction. The occurrence of sudden death has many explanations.[3, 26] It may be caused by myocardial infarction due to acute coronary occlusion or coronary insufficiency, severe cerebral ischemia, cardiac standstill, ventricular fibrillation, hypersensitive carotid sinus reflex or obstructing thrombi formed on the stenosed aortic valve.

SUMMARY

An effort has been made to correlate the clinical findings with the pathologic material in 22 cases of calcific aortic valve stenosis. For more accurate evaluation, cases with polyvalvular involvement were not considered. Rheumatic fever and arteriosclerosis have been definitely established as the etiologic factors. A sufficient number of cases of healed subacute bacterial endocarditis with calcification have been reported to consider this as a rarer cause and we have added another case to this group. The occurrence was four times greater in males than in females in the rheumatic group. Arteriosclerotic involvement occurred seven times more frequently among males. The average age in the arteriosclerotic group was 23 years more than in the rheumatic group. Dizziness and syncope were due to cerebral anemia caused by diminished output. The anginal attacks were due to myocardial ischemia. Left ventricular failure manifested itself frequently in varying degrees of dyspnea. The rheumatic group had a longer hospitalization period than the arteriosclerotic group.

Among the reasons for the failure to make an accurate diagnosis were the misinterpretation of the murmur, the confusion caused by the presence of other murmurs and the lack of corroborative findings, such as a systolic thrill and absence of an aortic second sound. The presence of apical murmurs during systole was either due to transmission from the base or due to a relative mitral insufficiency caused by the dilatation of the left ventricle. Presystolic murmurs at the apex were of the Austin-Flint type. The pulse pressure was usually normal or decreased, but was sometimes increased because of concomitant aortic regurgitation or hypertension, although it was frequently difficult to estimate because of radial artery sclerosis. Clinical enlargement of the heart closely paralleled the weight which was increased considerably. Fluoroscopic and roentgenographic examination is capable of almost doubling the average frequency of diagnosis which was 36.4 per cent in our series. Left axis deviation and T-wave negativity were helpful in differentiating aortic insufficiency and mitral lesions since these tend to produce hypertrophy in the right chambers as well, with resultant right ventricular strain. Three types of calcification in the aortic valve have been described. In the rheumatic type, calcification began in the ventricular aspect of the distal third of the cusps; whereas, in the arteriosclerotic types it began at the base of the aortic surface. The degree of calcification closely paralleled the degree of stenosis. Cardiovascular and extracardiovascular causes of death were about equally divided, but of the former pulmonary edema and congestive heart failure predominated. The possible occurrence of sudden death existed in five cases of arteriosclerotic origin but these may have been due to acute myocardial failure or pulmonary infarction.

Conclusion

In the absence of hypertension and definite mitral valve involvement, a systolic murmur at the aortic area should suggest calcific aortic valve stenosis. This possibility becomes greater in the presence of dizziness, precordial pain, regular sinus rhythm, cardiac enlargement and an absent second aortic sound. Roentgenologic and especially fluoroscopic studies, as well as electrocardiographic findings, may verify this. Many pitfalls in clinical diagnosis are evaluated and correlated with the pathologic findings. In the etiology of pure calcific aortic valve stenosis, arteriosclerosis is more than three times as important as rheumatic fever. The former factor is prevalent among males in an advanced age group, the latter among females averaging 23 years younger.

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ANEURYSMS OF THE ABDOMINAL AORTA*

By Joseph Epstein, 1st Lt., M. C., A. U. S.

Aneurysm of the abdominal aorta must be considered in the differential diagnosis of obscure abdominal disorders. Unfortunately, its identity is rarely established in the early period of development. In more advanced lesions, where only a vague mass lacking the features of vascular origin is found, it still may defy recognition. In such situations one must turn to the roentgenogram to help define the tumor and establish its character.

This report will review the available literature and add nine additional cases. In five the diagnosis was confirmed by postmortem examination. The incidence, etiology, pathology, clinical features and laboratory procedures of importance will be discussed.

Incidence. In 1903, Bryant,[1] reviewing 18,678 necropsies performed at Guy's Hospital between 1854 and 1900, found among 325 cases of aortic aneurysms 54 (0.28 per cent) of the abdominal aorta. Osler [2] noted 60 aneurysms in the first 2,200 necropsies performed at the Johns Hopkins Hospital, of which 11 occurred in the abdominal aorta, an incidence of 0.5 per cent. Of the 18,000 necropsies studied at the same institution over a 16-year period, 16 cases of abdominal aortic aneurysms were found, an incidence of 0.09 per cent. The ratio of abdominal to thoracic lesions was one to ten. In a statistical study by Lucke and Rea [3] in 1921 of postmortem studies made at the Philadelphia General Hospital and the Hospital of the University of Pennsylvania reviewing the years 1875 to 1916, there were 40 cases of aneurysms of the abdominal aorta in a total of 12,000 necropsies, an incidence of 0.3 per cent. Of 321 aneurysms, 173 were in the aortic arch, 31 in the thoracic aorta and 40 in the abdominal aorta. Gernert [4] reviewed 1062 autopsies and found six aneurysms of the abdominal aorta in a total of 28 aneurysms of all types. Kampmeyer [5] listed 68 cases of abdominal aneurysms, reporting a ratio of 1 to 7.8 of the abdominal to the thoracic types. Saleeby and McCarthy [6] in a study of 84 cases of aneurysms from the surgical service of the Philadelphia General Hospital found that of 74,629 admissions in a 32-year period, 47 aortic aneurysms were encountered. Of these, 14 were located in the abdominal aorta and 33 in the thoracic aorta. In 1941, a comprehensive review of the subject by Ruffin, Castleman and White [7] included 9,600 necropsies at the Massachusetts General Hospital since 1897. Of 116 aneurysms, 20 were in the abdominal aorta.

The varying incidence of abdominal aneurysms in different geographic localities was first noted by Osler.[2] Lucke and Rea [3] concluded that aortic aneurysms were more frequent in the United States and Great Britain than in the Teutonic countries.

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It is significant that the ratio of abdominal to thoracic aneurysms has undergone a change from 1 to 10 (Osler, 1905), 1 to 5.1 (Lucke and Rea, 1921), 1 to 7.8 (Kampmeyer, 1936) to values of 1 to 2.8 (Saleeby and McCarthy, 1938), and 1 to 3.3 (Ruffin, Castleman and White, 1941). A declining incidence of aneurysm due to syphilitic aortitis and an increasing incidence of arteriosclerotic aneurysms is suggested by these figures.

Distribution. Abdominal aortic aneurysms occur most often in males. Bryant [1] noted that 90 per cent of his 54 patients were men, as were 14 of Osler's 16 cases. Keen [15] states that the frequency of abdominal aneurysms in the male is 11 times that in the female.

Age. Nine of Osler's 16 cases were under 40 years of age, and in three the disease appeared before the thirtieth year.[2] Bryant [1] found that 63 per cent of his 54 patients were under 40, and two were under 20 years of age. Ruffin, Castleman and White [7] observed the age at death to average 46.4 years in their syphilitic patients, whereas in 23 cases described as arteriosclerosis and senile ectasia the average age at death was 72.7 years. Kampmeyer [5] found that 46 of his 68 cases were less than 45 years of age. There is general accord as to the age distribution of the two major groups of aneurysms, the syphilitic occurring in the fourth and fifth decades and the arteriosclerotic in the sixth and seventh.

Etiology. The etiology of aneurysms of the abdominal aorta has been ascribed principally to syphilis and arteriosclerosis, either independently or together. Other etiologic factors include trauma, such as perforating abdominal gunshot or stab wounds, contiguous extra-arterial disease with secondary injury to the vascular wall, inflammatory vascular lesions such as tuberculosis, streptococcus infections and rheumatic fever.[8, 9, 10, 19] The history of a chancre and a positive Wassermann reaction assist in establishing the etiology. However, the serologic reactions may be negative in some patients manifesting evidence of syphilitic infection both grossly and microscopically.[8]

Syphilitic mesarteritis has been considered the primary cause of sacculated and multiple aortic aneurysms, whereas arteriosclerosis is associated with the fusiform or diffuse type. The distribution of the various aneurysms was described by Ruffin, Castleman and White [7] who studied 66 aneurysms in the thoracic and 20 in the abdominal aorta. Of these 66 thoracic lesions, 60 were syphilitic and three arteriosclerotic. Three were classified as senile ectasia in which dilatation of the vessel occurred without evidence of arteriosclerosis or syphilis. Of the thoracic aneurysms, 21 occurred in the ascending aorta, 37 in the arch, and eight in the descending thoracic portion. Of the 20 abdominal aneurysms, three were syphilitic and 17 arteriosclerotic in origin.

Pathology. Aortitis is the most frequent lesion of tertiary syphilis and may be its sole manifestation.[11] The saccular aneurysm characteristic of the disease is the result of an inflammatory process which begins as a mesarteritis.

Microscopically, patchy areas of lymphocytic infiltration form about the vasa vasorum in the media and adventitia. Tissue destruction is rapid and the dissolution of normal architecture, which is more profound than in arteriosclerosis, results in scarring and subsequent ectasia. A fibrous adventitia of varying thickness eventually forms the aneurysmal wall. The sac often contains a laminated thrombus in which organization rarely occurs.

In arteriosclerotic aneurysms the arterial wall is weakened throughout because of progressive medial changes. After the elastic fibers degenerate, they are replaced by fibrous hyaline tissue, a non-inflammatory process in which the change progresses from the intima to the adventitia. The extent of this replacement has been evaluated by Krafka [9] who found a loss of 70 per cent of the aortic elasticity in elderly patients because of degenerative changes. In arteriosclerosis these changes progress from intimal thickening to the deposition of atheromatous plaques which may eventually ulcerate. The media is slowly replaced by connective tissue leaving a thickened, sclerotic adventitia as the sole supporting structure. The progressive dilatation of the vessel as a result of these changes reflects its inability to resist intravascular tension.[10]

Dilatation of the aneurysm from the constant strain may eventually terminate in rupture at a point near the origin of the sac at the aorta, an area of minimal resistance.[12] The frequency of rupture as a terminal event was emphasized by Kampmeyer [5] who found that 31 of 38 patients examined post mortem expired in this manner. No statistics showing the relative frequency of rupture in syphilitic as compared to arteriosclerotic aneurysms were available. Of the five aneurysms studied at autopsy in the present series, one of the two syphilitic aneurysms and two of the three arteriosclerotic aneurysms ruptured.

The site of election of abdominal aortic aneurysms is near the celiac axis. The areas just below the diaphragmatic hiatus and above the iliac bifurcation are sometimes affected.[5, 13, 14, 15] The regions of relative weakness in the abdominal aorta exist because of the loss of diaphragmatic support immediately below the hiatus and because of the sudden alteration in blood pressure occurring near the origin of the large vascular trunks.[2]

Erosion of the vertebral bodies occurs because of a chronic inflammatory reaction produced in the cancellous bone by the pressure of the enlarging aneurysm. The cartilage, being avascular, does not show this reaction and consequently is preserved. The crescentic shaped areas of resorption proximal and distal to each disk are a result of the support given to the sac by the intervertebral disc and the subsequent relief of pressure on adjoining bone (figures 1, 6).[13] Osler suggested that the yielding nature of cartilage played an important rôle in its preservation.[2]

The twelfth thoracic and the first two lumbar vertebrae are most frequently eroded. The left anterior aspect is the earliest site of resorption, a phenomenon explained by the position of the aorta at these levels.[16]

FIG. 1. *Case 1.* Right oblique exposure of the spine showing destruction (scalloping) of the bodies of the twelfth thoracic and first lumbar vertebrae by an aneurysm of the abdominal aorta.

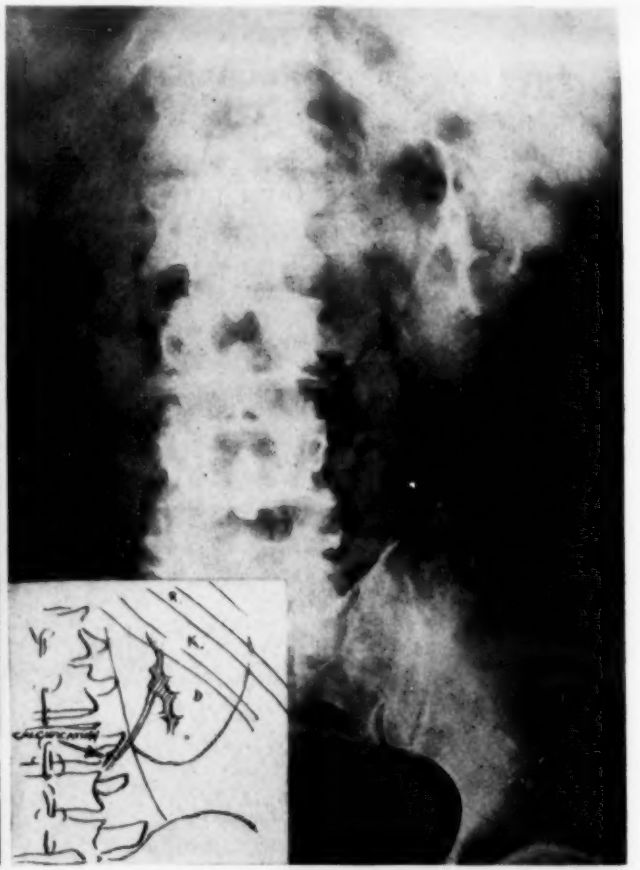

FIG. 2. *Case 3.* Intravenous pyelogram showing lateral displacement and angulation of the right ureter at the level of the third lumbar vertebra. A lunear area of calcification is seen above the site of angulation parallel and just medial to the ureter.

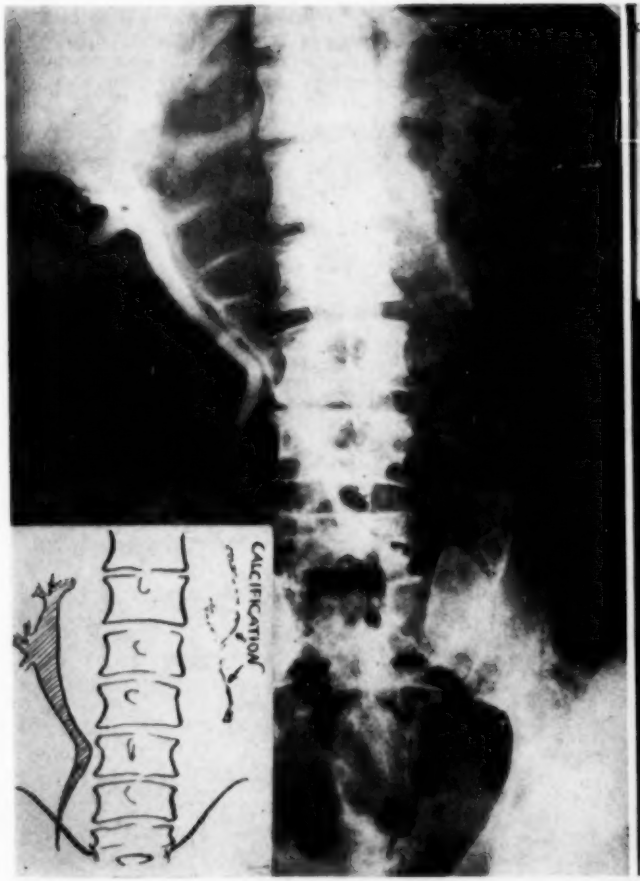

FIG. 3. *Case 5.* Intravenous pyelogram showing lateral displacement and angulation of the right ureter. Linear areas of calcification may be seen to the left of the spine.

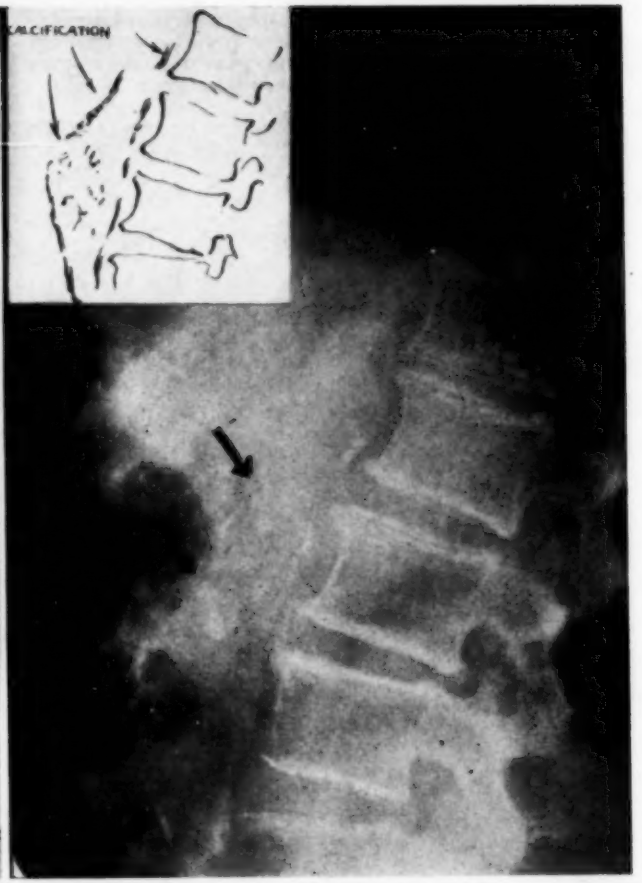

FIG. 4. *Case 7.* Calcification in the wall of an aneurysm of the abdominal aorta anterior to the second, third and fourth lumbar vertebrae.

Linear areas of calcification may be seen to the left of the spine.

and fourth lumbar vertebrae.

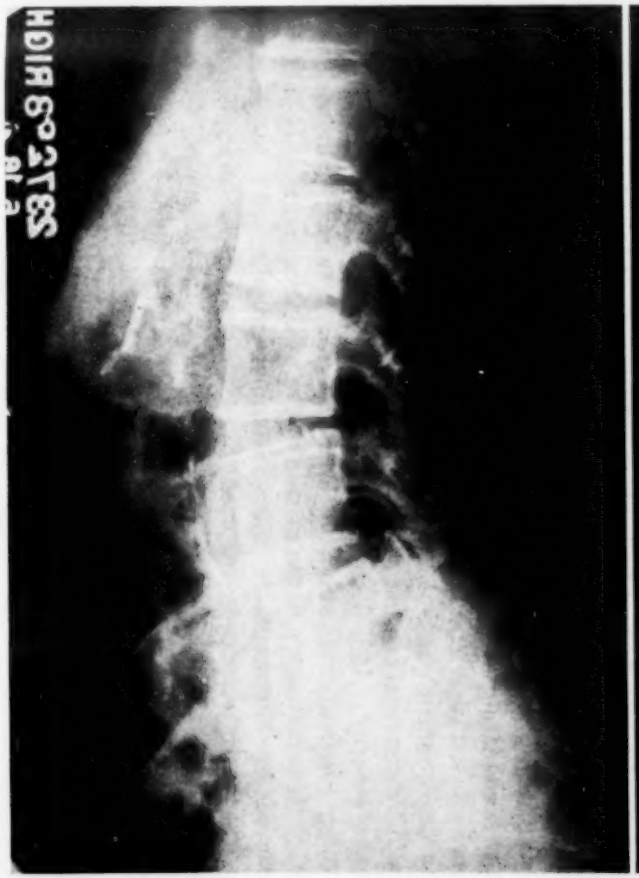

FIG. 5. *Case 9.* Calcification in the wall of an aneurysm of the abdominal aorta anterior to the third and fourth lumbar vertebrae.

FIG. 6. Erosion of the thoracic and lumbar vertebrae by an aneurysm of the aorta confirmed at autopsy. Scalloping is unusually well demonstrated.

Subsequent resorption of bone results in the exertion of pressure on nerve roots and in extreme cases on the spinal cord causing paraplegia. The lowermost ribs as well as the transverse processes of the vertebrae may also be eroded.

Displacement or distortion of organs commonly occurs as the aneurysm enlarges. The diaphragm may be elevated, thereby changing the cardiophrenic angles. The stomach may be indented, or the kidneys and ureters displaced, the latter at times being obstructed. The left ureter and kidney are affected with notable frequency. As a result of rupture followed by retroperitoneal and intraperitoneal hemorrhage, a number of distorting phenomena of the viscera may occur. By means of further extension beneath fascial planes, the subcutaneous tissues in the lumbar region and over the dorsum penis may eventually be reached.[16, 17] Rupture may occur into the pleural cavity, the mediastinum or the gastrointestinal tract.[19] Intestinal obstruction, both mechanical and paralytic, has been produced by this mechanism. Portal, splenic and mesenteric vein thrombosis have been reported.[2, 17] Rupture of the aneurysmal sac may result in sudden death due to a single massive hemorrhage. Terminus may be delayed if bleeding is intermittent. When this occurs the retroperitoneal connective tissue structures about the aneurysm confine the extravasated blood, and by this tamponading effect death may be delayed until the final, exsanguinating hemorrhage.[16] The extent of the fascial planes about the aorta has been clearly outlined by Congdon.[18]

Symptoms. Aneurysms of the abdominal aorta are notorious for the latency of their clinical expressions. Pain of a varying nature and intensity is the predominating symptom. It may be caused by hemorrhage into the perirenal space, by vertebral erosion, by pressure on the dorsal nerve roots, and by displacement of the kidney and ureter with obstruction. The pain produced by vertebral erosion and dorsal root pressure is neuralgic and is of increasing severity. It is described as boring and piercing and is usually excruciating. Infrequent cases have been reported in which pain has been absent.[13] It is refractory to the usual sedative measures and may be induced or relieved by alterations in intra-abdominal pressure and by postural changes.[13, 16] In one case reported by Uhle[16] exertion precipitated a paroxysm of pain which was relieved when the patient assumed the erect position. Sitting and lying prone made the pain unbearable.

The pain radiates in a characteristic fashion, frequently simulating renal colic. This has resulted in the diagnosis of primary urologic disease more often than aneurysm. The report published by Uhle[16] presents outstanding examples of this phenomenon.

Depending upon the size of the sac and its location, the pain may be referred to the lower abdominal wall, the groin, testes and inner aspect of the thigh and knee along the distribution of the obturator and genito-femoral nerves. Pain may also be referred to the lumbosacral region and hip.

When the vascular wall gives way and intermittent hemorrhage occurs, the pain is recurrent like that of renal colic. Since slow leakage may exist for weeks prior to the terminating episode, the two conditions may be readily confused. Nausea and vomiting are more frequent in patients who have an accumulation of retroperitoneal blood, and loss of weight and fever are common. Pain due to vertebral erosion and nerve root pressure rarely shows these characteristics.[16] When rupture and massive hemorrhage take place, the patient may suddenly feel something give way and may experience terrific pain soon followed by shock. Occasionally, a pulsating mass accompanied by a thrill and bruit may be found following this type of hemorrhage.

The duration of symptoms seldom exceeds one year. In the 57 cases reported by Kampmeyer,[5] 35 had symptoms lasting six months or less and in 51 patients symptoms had been present no more than one year.

Physical Findings. The cardinal physical finding, when present, is an abdominal mass which is usually located in the epigastrium. It may be situated elsewhere in the abdomen, occasionally in the left subcostal region or in the loin. The mass characteristically transmits an expansile pulsation. A thrill and bruit may be noted. Kampmeyer [5] observed pulsations in 49 of the 50 patients who had an intra-abdominal tumor. A diminished volume of the crural pulse retarded in relation to the radial pulse has been observed. The presence of a large amount of blood clot about a perforated, intermittently bleeding aneurysm disguises the lesion because it effectually prevents the transmission of the vascular impulse, thrill and bruit. The tumor, however, may be prominent.

In addition to the mass, ecchymotic areas may be present over the lumbar areas. Tenderness and muscle spasm are indications of the extent of hemorrhagic infiltration. The presence of shock is of little aid in early diagnosis. In the absence of a palpable mass, the clinical diagnosis is very difficult. The history is valuable in cases of this type because it may suggest the diagnosis or render its exclusion mandatory.

Differential Diagnosis. The differential diagnosis involves many surgical and medical conditions, chiefly renal and extrarenal diseases. Frequent displacement of the kidney and ureter occurs because of the pressure of a dilating aneurysm and because of hemorrhage into the perinephric space. The symptoms associated with vertebral erosion and nerve root pressure may further confuse the clinical picture.

Pain produced by aneurysm of the abdominal aorta, although possessing many of the characteristics of renal pain, is rarely relieved by antispasmodics or opiates. Peritoneal irritation due to hemorrhage produces signs almost typical of an acute abdominal condition and surgical intervention may appear unavoidable. The presence of a pulsating mass is very significant, and signs of progressive internal bleeding are of further aid.

From the roentgenologic point of view, hemorrhage into the perirenal space may be confused with perinephric abscess by obscuring the visualization

of the kidney and psoas shadows. Evidence of continuous blood loss, as well as the abrupt onset of symptoms associated with a mass, argues against this diagnosis. The insertion of a needle into the suspicious area may establish the diagnosis.

Intra-abdominal tumor large enough to be either palpated or visualized roentgenographically occasionally must be differentiated from aneurysm, especially if adjacent to the aorta. In this group are gastric carcinoma, pancreatic cysts, masses of retroperitoneal lymph nodes and renal tumors.

Indentation of the posterior aspect of the stomach and symptoms pointing to an intrinsic gastric lesion may be present when an aneurysm presses against the stomach. In gastric carcinoma, however, if not immobilized by extragastric extension, movement of the mass synchronous with respiration may be felt. It may be difficult to differentiate between the two lesions without the presence of vertebral erosion or the presence of an expansile pulsation in the mass. Laboratory tests may be indecisive (Case 1).

Pancreatic cysts may simulate aortic abdominal aneurysms by transmitting the vascular pulsation. Both lesions may displace the stomach anteriorly and both may contain calcific deposits. The differentiation, therefore, may at times be made only by detecting vertebral erosion or by careful study of the pulsation and recognition of its transmitted character.[5]

Differentiation from a mass of malignant retroperitoneal lymph nodes may be difficult because not only may the mass pulsate, but vertebral erosion may occur.[5] The intervertebral disks, however, are destroyed in malignant diseases and the vertebrae involved present an irregular, patchy, ragged outline with a worm-eaten appearance, findings not associated with erosion due to aneurysm.

Other pathologic entities which may be simulated by abdominal aortic aneurysms include retroperitoneal sarcomata, gumma of the liver and omental tumors. The symptoms of tabetic crises, cholecystitis and cholelithiasis, lead colic, neuritis and peptic ulcer all have been closely imitated. Intestinal obstruction has been produced mechanically by this lesion and the pain has been observed to precipitate meteorismus.

Roentgenographic Findings. The diagnosis of aortic aneurysm may be facilitated by the use of various roentgenographic technics. Although not revealed directly in all cases, the aneurysm may indicate its presence by the diverse changes the expanding lesion produces on contiguous organs and skeletal structures. Several technics have been described to provide maximal acuity and definition. The protrusion of an aneurysmal sac ventrally and to the left predicates that the best evidence of bone resorption will be seen in lateral and lateral oblique projections (figures 1, 6). The intervertebral disks are never destroyed. The transverse processes and the lowermost ribs may show areas of resorption. Vertebral erosion in the presence of the senile, arteriosclerotic aneurysm has not been evidenced in any of the cases in the present series. This negative finding has not been mentioned

in other reports, although it may be significant. The calcified aneurysmal wall following the line of least resistance presents an anterior and lateral bulge (figures 2, 3, 4, 5).

Direct roentgenographic examination of the abdomen may reveal the arteriosclerotic wall of an aneurysm as a thin curved line of calcification lateral and anterior to the vertebral column (figures 2, 3, 4, 5). Further definition may be necessary in order to establish the diagnosis. Additional contrast in the abdominal cavity may be acquired by distending the stomach with air, by producing a pneumoperitoneum or by inflating the colon.

The tumor mass is rarely of sufficient size and density to be revealed in the anteroposterior roentgenogram of the abdomen. This is particularly applicable to aneurysms located between the diaphragm and the origin of the renal arteries. Their presence may be revealed by the methods of gastric inflation and pneumoperitoneum. A filling defect of the cardiodiaphragmatic angles or obliteration of the psoas margins may occur.[16]

The frequency with which symptoms of an abdominal aortic aneurysm have been confused with renal disease makes the use of retrograde and excretory urography essential. Since the kidney and ureter are often displaced by an aneurysm, as has been evidenced by many postmortem examinations, the radiologist must employ urography in the investigation of abdominal aortic lesions. Five cases revealing this phenomenon of displacement have been reported within the last three years.[8, 16, 17] To these two additional cases are added.

Case Reports

Case 1. C. J., a 73 year old colored janitor, was admitted because of pain in the left lower quadrant and left loin for two months. The pain was sudden in onset, sharp, intermittent and of increasing severity. He had been completely incapacitated for one month before admission. Excessive indulgence in alcoholic beverages increased the severity of his symptoms. He had lost 15 to 20 pounds during this period. There were no symptoms referable to his pulmonary, cardiovascular, gastrointestinal or genitourinary systems.

He had had syphilis 25 years before and gonorrhea on two occasions. Treatment had been received for both conditions.

At examination the patient was in no distress. He was poorly nourished. His blood pressure was 140 mm. Hg systolic and 100 mm. diastolic, temperature was 102° F., pulse 90, respirations 28. His sclerae were icteric. The abdomen was scaphoid and epigastric tenderness and spasticity were elicited. There was tenderness in the left lower quadrant extending from the crest of the ilium downwards and mesially. Definite bilateral costovertebral tenderness was found. The liver edge was palpated one finger's-breadth below the costal margin.

The cerebrospinal fluid was clear. The Wassermann reaction was positive and the colloidal gold curve was paretic.

Gastric analysis revealed a trace of blood in all specimens and achlorhydria. No lactic acid was present.

Direct roentgenographic examination of the abdomen revealed no evidence of renal disease. An intravenous urogram was normal. Examination of the stomach revealed a filling defect at the cardia interpreted as a neoplasm.

His course was progressively downward. He became mentally sluggish, emaciated and developed urinary and fecal incontinence. He died 31 days after admission. The clinical diagnoses were cirrhosis of the liver, gastric carcinoma, lues and pyelonephritis.

Postmortem examination revealed an aneurysm of the abdominal aorta with erosion of the twelfth thoracic and first lumbar vertebrae. The thoracic aorta, especially the arch, showed longitudinal wrinkling. The abdominal aorta just above the renal arteries presented a sacculated aneurysm measuring 8 by 8 cm. In the posterior wall of the aorta at this level an oval opening leading into the aneurysm was found. The wall was thick and composed of laminated layers of brown material. Extensive vertebral erosion was present; only a thin shelf of bone remained between the aneurysm and the spinal cord. A generalized miliary tuberculosis was the immediate cause of death.

Reëxamination of the roentgenograms of the stomach taken in the oblique positions revealed scalloping of the bodies of the twelfth thoracic and first lumbar vertebrae. There was no evidence of vascular calcification (figure 1).

Case 2. A. K., a 58 year old white man, was admitted with chills, fever up to 104° F., and cough for three weeks. Four days prior to admission his right foot had suddenly become numb and painful. There were occasional episodes of vomiting. Early in the course of his illness he complained of mild epigastric pain radiating to the left shoulder and to the left lower quadrant. There was no weight loss. His past history was not contributory.

Physical examination revealed an acutely ill, well developed and well nourished man. His blood pressure was 92 mm. Hg systolic and 60 mm. diastolic, his pulse was 120, and his temperature was 105° F. His left pupil was irregular and smaller than the right. His lips were herpetic and the tongue showed atrophy of the papillae. Examination of the chest revealed moist râles at both bases. The heart was slightly enlarged to percussion. There was a normal sinus rhythm and a soft apical systolic murmur. The liver was enlarged two fingers'-breadth below the costal margin and was tender. There was tenderness to percussion over the right costovertebral angle. The right foot showed diminution in pain, touch, temperature and position sense. Vibratory sense was absent. The plantar reflexes were decreased. Pulsations in the right popliteal artery and its distal branches were absent.

The blood Wassermann reaction was reported as positive. Blood and stool cultures for *Salmonella cholera suis* were positive as were agglutination tests for Paratyphoid A and B. The Widal test was positive. Repeated urine examinations were negative.

Roentgenographic examinations of the abdomen and chest were reported as negative.

The patient's temperature subsided soon after hospitalization, and he obtained considerable relief from the uncomfortable sensations in his right foot. There was definite rubor on dependency of his toes, more evident on the right. On one occasion a shower of petechiae was observed over the plantar aspect of his right foot.

He was fairly comfortable until 10 days before death, when he began to complain of persistent and severe back pain. This was followed by abdominal distention. At this time no masses or organ edges could be palpated. Developing the typical signs of shock he died on his fifty-sixth hospital day.

Postmortem examination revealed approximately 100 c.c. of free blood in the peritoneal cavity. There was an extensive hematoma beneath the posterior abdominal parieties on the left side. The small and large intestines were markedly distended, and there were adhesions between the loops of bowel and between the bowel and the liver.

Just above the bifurcation of the abdominal aorta the vessel was dilated, forming a large globular mass. The posterior wall of the aorta was destroyed and replaced by a blood clot. There was calcification and "tree-barking" in the arterial wall.

The diagnosis of aneurysm of the abdominal aorta was not made ante mortem. Suggestions offered to explain the back pain and ileus were osteomyelitis of the sacrum and rupture of an abdominal viscus. The symptoms in the right foot were believed due to arteriosclerosis obliterans with recent insult to one of the collateral vessels and subsequent recovery. The presence of the Salmonella infection overshadowed the symptoms of the aortic lesion during the greater part of his illness. Death was caused by rupture of the aneurysm.

Reëxamination of the roentgenograms of the lumbar spine in the lateral view showed the presence of a dilated abdominal aorta, fusiform in shape, extending from the level of the second to the fourth intervertebral disks with the widest diameter (5 cm.) at the level of the third. Identification was made possible by the calcification in the arterial wall. No erosion was seen. The postero-anterior views were of no value in demonstrating the lesion.

Case 3. H. R., a 78 year old man, was admitted because of pain in the right lumbar region. His present illness started four months before admission with weakness, a slight cough, and chest pain. Unusual frequency of urination and difficulty in starting the urinary stream were also present. Forty years before he had had tuberculosis.

Eight days before admission he had a sudden attack of pain in the right upper quadrant radiating to the back beneath the right shoulder blade. Three days later he was admitted to another institution where a mass was palpated in the right lumbar region. This was aspirated and a cloudy fluid loaded with pus was obtained. No bacteria or acid fast organisms were found. Urinalysis was negative.

On admission he appeared dehydrated and chronically ill. His blood pressure was 150 mm. Hg systolic and 100 mm. diastolic. The heart sounds were distant and frequent extrasystoles were present. The abdomen was protuberant, and no masses or viscera could be palpated. There was tenderness in his right hypochondrium and in the right lumbar region.

His course was steadily downward. Intravenous urography revealed good excretion from both kidneys. The right kidney was smaller than the left. A chest roentgenogram showed the heart to be normal. A gastrointestinal series was not contributory. No serologic reports were available.

Abdominal paracentesis yielded about 5,000 c.c. of clear fluid. No neoplastic cells were found in the sediment. Following this procedure an orange-sized, moveable, tender mass could be felt in the epigastrium to the left of the midline.

The patient became progressively weaker, drowsy and uncoöperative. Anorexia was severe, hiccuping and vomiting became frequent and abdominal distention more apparent.

The clinical diagnoses were possible right perinephric abscess, gastrointestinal malignancy, arteriosclerotic heart disease and chronic bronchitis.

At postmortem examination miliary tuberculosis was found to be the primary cause of death. Five cm. distal to the orifices of the renal arteries there was a globular distention of the aorta measuring 8 cm. in diameter. The lumen was filled with a rubbery, gray-yellow mass adherent to the vessel wall but not causing occlusion. Numerous large atheromatous plaques, many of them ulcerated, were present in the ascending and descending thoracic aorta.

Reëxamination of the intravenous pyelograms yielded the additional information that although the kidney shadows were normal, there was a lateral displacement of the right ureter in its upper third. A thin line of calcification could be seen medial

and parallel to the ureter just above the site of ureteral angulation at the level of the inferior margin of the third lumbar vertebra (figure 2).

The presence of this calcific deposit together with the slight displacement and angulation of the upper right ureter might well have suggested the correct diagnosis.

Case 4. S. C., a 76 year old man, suddenly had nausea, vomiting, belching and severe pains in his right loin radiating towards the midline. There was an accompanying desire to defecate but no stools were passed. The pain lasted 12 hours, after which the patient collapsed. Two years before the patient had had a similar but more brief attack.

Examination revealed an aged, poorly-nourished, feeble man. Sonorous and crepitant râles were heard at both lung bases posteriorly. The liver was palpable one finger's-breadth beneath the costal margin. An indistinct ballottable mass was palpable in the right upper quadrant. Marked right costovertebral tenderness was present. There was moderate abdominal rigidity but no rebound tenderness. His blood pressure was 106 mm. Hg systolic and 50 mm. diastolic. The urine was negative save for 2 plus albumin and many urate crystals. The sedimentation rate was 80 mm. in one hour. The Kline reaction was negative.

A roentgenogram of the abdomen was reported as negative. Roentgenographic examination of the chest revealed an infiltrative lesion involving the lower half of the right lung consistent with the diagnosis of pneumonia.

The patient was somewhat more alert the day after admission. At this time he described his pain as originating in the right loin and radiating anteriorly across the epigastrium. Incontinence was present. His temperature rose to 101° F., and on his third hospital day he died.

The clinical diagnoses were right renal calculus, coronary occlusion and perforated viscus.

At postmortem examination there was an aneurysm of the abdominal aorta that had ruptured producing an extensive retroperitoneal hemorrhage and hemoperitoneum. There were approximately 500 c.c. of bloody fluid in the peritoneal cavity. The entire retroperitoneal area, particularly on the right side, was purple red in color owing to extravasated blood. Blood was also present between the leaves of the mesentery. Just above the bifurcation of the aorta and 4 cm. below the renal arteries there was a fusiform dilatation of the aorta measuring 8 cm. in diameter. Two cm. below the origin of this dilatation there was a jagged rupture of the aorta to the right of the midline measuring 1.5 cm. The aneurysm contained a friable, laminated clot 1.5 cm. thick which was attached to its wall. The arterial lumen was 2 cm. in diameter. Marked arteriosclerosis was evident in the aorta. Signs of vascular syphilis both grossly and microscopically were absent.

A review of the roentgenogram of the abdomen revealed several thin small areas of calcification to the right of the bodies of the first, second and third lumbar vertebrae close to the tips of the transverse processes. At first no significance had been attached to this observation, but in the light of the postmortem findings they assumed a most important diagnostic meaning inasmuch as they represented the lime salt deposits in the wall of the aneurysm.

Case 5. M. H., a 63 year old man, complained of pain in the right lumbar region for one week. Thirteen years ago he had had "trouble" with his right kidney. He had had hypertension for the past seven years. Three years ago he was hospitalized because of hematuria, nocturia and frequency. At that time a retrograde right pyelogram had been reported as normal. The discharge diagnosis then was prostatism and pyelonephritis.

Two weeks prior to admission he had a sudden onset of weakness, vomiting, epigastric pain and pain in the region of the right kidney. During the past nine days there had been increasing constipation. For the five days before admission

the most prominent symptom was pain in the right lumbar area radiating to the epigastrium and around the iliac crest to the scrotum. During the week before admission his temperature had varied between 101° and 102° F.

Physical examination revealed his heart and lungs to be normal. His abdomen was distended, tense and tympanitic. Tenderness was elicited in the right upper and lower quadrants, and there was a positive right Murphy sign. His blood pressure was 145 mm. Hg systolic and 90 mm. diastolic.

Three days after admission edema of the right lateral abdominal wall was noted. His breath became uriniferous. On the fourth day there was a question whether a palpable mass was present in the right upper quadrant. Two attempts to aspirate the right kidney were unsuccessful. A mass was definitely palpated in the right lower quadrant on the seventh day. Laparotomy through a right lower quadrant incision revealed a large retroperitoneal hematoma. Soon thereafter anuria developed and persisted until death three days later.

Urinalysis on admission revealed 4 plus albumin with numerous casts. A progressive anemia developed, the hemoglobin falling from 84 per cent to 56 per cent and the red cell count from 4.2 millions to 3.3 millions. The blood serologic reaction was negative. The urea nitrogen rose from 33 to 190 mg. per cent. The creatinine rose from 2.6 to 13 mg. per cent.

Anteroposterior roentgenograms of the abdomen revealed linear areas of calcification 3 to 4 cm. to the left of the bodies of the eleventh thoracic to the fourth lumbar vertebrae outlining a localized dilatation of the aorta with remarkable clarity. Retrograde pyelography demonstrated a lateral displacement of the right kidney and ureter opposite the first and second lumbar vertebrae, with angulation of the ureter at the level of the third lumbar vertebra. There was no ureteral obstruction (figure 3).

Wound inspection post mortem revealed a mass of clotted blood in the peritoneal cavity. A retroperitoneal hemorrhage infiltrating the posterior portion of the fat capsule of the right kidney was present. This infiltration extended from the upper pole of the right kidney to the retroperitoneal tissues in the lesser pelvis. At the level of the renal arteries there was a saccular aneurysm the size of an orange containing an organized laminated thrombus. At the lower end of the dilatation an intimal tear 2 cm. in diameter was seen opposite the retroperitoneal hematoma. The renal arteries were patent, but compressed and surrounded by the thrombus. Atherosclerosis of the aorta and moderate nephrosclerosis were present.

Case 6. S. N., a 56 year old man, was admitted because of nocturia, dysuria and pain in the lumbar region radiating anteriorly to the right groin of one week's duration.

When 15 years old the patient had a penile ulceration which was not treated. There was a history of hypertension for two years.

On admission the patient was a well developed man who did not appear to be ill. His lungs were normal. The heart was moderately enlarged to the left, and his blood pressure was 208 mm. Hg systolic and 98 mm. diastolic. The abdominal viscera were not palpable. A firm, non-tender mass about 7 cm. in diameter was felt in the left umbilical region extending one or two cm. below and to the left of the umbilicus. An expansile pulsation was noted, and the mass was well circumscribed and appeared to be part of the aorta. A loud bruit was heard transmitted towards the left common iliac artery. The left femoral artery was not palpated. Pulsations of the right femoral artery were full. The blood pressure in his right lower extremity was 240 mm. Hg systolic and 150 mm. diastolic, in the left zero. The entire left leg was cold. Shock tenderness was present over the right costovertebral angle. The Wassermann and Kline reactions were negative.

Roentgenographic examination of the abdomen revealed both kidneys to be normal. No calculi were seen. Hypertrophic changes were present in the lumbar vertebrae. A roentgenogram of the chest was normal. Repeated studies of the lumbar spine failed to reveal erosion of the lumbar vertebrae.

The patient's symptoms subsided and he was discharged with the diagnosis of an aneurysm of the abdominal aorta. The mass did not undergo any change.

Although repeated blood and cerebrospinal fluid Wassermann reactions were negative, he was placed on potassium iodide therapy. For the next 11 months he was asymptomatic. Soon thereafter he was readmitted because of sticking pains in his left upper quadrant radiating to the lumbar region and to the right upper quadrant. The pain was sudden in onset, and was relieved by bed rest.

Examination at admission showed that the patient had lost considerable weight. The abdominal mass was described as about 8 cm. long, vaguely outlined, non-tender, and located to the left of the umbilicus. The left femoral pulsation was barely palpable.

The Kline reaction was negative. Blood and urine studies were normal. The patient was discharged one week after admission.

A review of the roentgenograms made at his last admission revealed a thin calcific shadow in the wall of the abdominal aorta outlining a fusiform aneurysm. The widest diameter was at the level of the fourth lumbar vertebra. The calcification could be seen only in the lateral projection.

Case 7. H. K., a 64 year old man, was admitted because of back pain for 10 days. For the past nine years he had had anginal attacks. Two years previously he had been bedridden for six months following a coronary occlusion. There was also a past history of ankle edema and intermittent claudication for eight years while orthopnea and a chronic cough had been present for two years.

During the 10 days before admission he had a dull, severe, almost continuous non-radiating pain in the left lumbar region which increased in severity after eating. Relief could be had by drinking milk during the early part of his illness. He later observed that the pain was alleviated by assuming the recumbent position.

Examination revealed a poorly-developed white man who appeared to be comfortable. His heart and lungs were not remarkable. The abdomen and breasts were large, pendulous and of a feminine type. No organ edges or masses were noted. Lumbar tenderness was marked and very slight left flank tenderness was elicited. There was a marked dorsal kyphosis. Pubic hair was almost absent and his testes were small.

The diagnosis on admission was a polyglandular syndrome of the hypogonadal type. A neoplasm or cyst of the pancreas was considered.

Roentgenograms of the lumbar spine revealed moderate hypertrophic osteoarthritis. In the lateral projection it was possible to demonstrate calcification in the abdominal aorta outlining a fusiform dilatation extending from the second lumbar intervertebral space to the center of the body of the fourth lumbar vertebra. The greatest diameter, 4 cm., was seen at the level of the body of the third lumbar vertebra. Both the anterior and posterior walls of the calcified vessel were seen in the lateral projection. The dilatation was principally anterior, the posterior wall being straight. There was no bone erosion (figure 4).

The diagnosis of a calcified aneurysm of the abdominal aorta was considered established. The roentgenographic findings were the only means of identifying the lesion accurately inasmuch as neither the history nor clinical findings at the time suggested its presence.

Case 8. D. P., a 67 year old white man, was admitted because of recurrent pains in the lumbar region radiating down the right thigh for nine weeks. The onset of these attacks was sudden, and the pain was described as sharp. The attacks lasted

from one to one and one-half hours, and recurred at intervals of from one to three days. The last episode occurred the day of admission after a remission of about four days.

Six years ago he had had a coronary thrombus following which his activity was restricted. Symptoms of prostatism had been present for two years. No history of syphilis was elicited.

On physical examination his heart was not enlarged. A short, soft systolic murmur was heard over the mitral area. His blood pressure was 170 mm. Hg systolic and 110 mm. diastolic. The abdomen was soft. A large, firm, smooth, nontender, elliptical mass was palpated in the right lower quadrant. It was deeply fixed and transmitted an expansile impulse synchronous with the heart beat and appeared to be continuous with the aorta. No lumbosacral or sacroiliac tenderness was present. There was moderate atrophy of the right lower extremity most evident in the thigh. Rectal examination revealed a symmetrically enlarged, soft, tender prostate. Neurologic examination was negative except for motor weakness of the left lower extremity and a positive Lasègue's sign on the right side. The blood and cerebrospinal fluid serology were negative.

Roentgenographic examination of the lumbar spine and pelvis revealed advanced osteoarthritic changes affecting the first and second lumbar vertebrae. Intravenous urography showed both kidneys to function normally. The lower portion of the right ureter was not visualized; the upper portion was normal.

An air contrast enema study of the colon failed to reveal any local pathologic lesion. There was, however, a slight increase in density over the right wing of the sacrum. Whether this was due to the pulsating mass noted on physical examination could not be stated with certainty. It was noteworthy that a roentgen-kymogram taken after the rectal instillation of air showed pulsations in this region synchronous with the heartbeat.

Laminagraphic studies of the abdomen were not helpful. A pneumoperitoneal study was reported as follows: "in the right abdomen above and overlying the inner margin of the ilium, as well as the adjacent portion of the sacrum, there is a semiopaque mass which on oblique study apparently projects slightly forward. Though one cannot state exactly its true nature, I am inclined to believe from its tapering appearance and the fact that it pulsates that we are dealing with an abdominal aneurysm of the lower aorta."

The discharge diagnosis based on clinical and roentgenologic evidence was an aneurysm involving the abdominal aorta and right iliac artery.

Case 9. Z. L., a 74 year old white woman, was first seen at the Hospital in 1939 for an acute hemorrhagic cystitis. She also had hypertension and a large umbilical hernia. Subsequent admissions in 1941 and 1942 for recurrence of the cystitis and pyelonephritis were recorded. In the course of radiographic examination of the lumbar spine a markedly calcified abdominal aorta was found with a definite anterior bulge indicative of aneurysmal dilatation. No masses or palpable viscera were noted. The Kline reaction was negative.

The roentgenograms revealed the aneurysm to be fusiform in shape, extending from the second to the fourth lumbar intervertebral spaces, the widest diameter being at the level of the third. The anteroposterior roentgenograms were of no aid in defining the lesion. The vertebral bodies were intact (figure 5).

In this case the aneurysm was found in the course of routine roentgenographic examination.

Discussion

The correct diagnosis was made in four of the nine cases reported here. There were eight men and one woman in the series. The symptoms pro-

duced by the lesion were mostly those suggestive of renal disease, resulting in the diagnosis of renal calculus, pyelonephritis and perinephric abscess. Gastrointestinal malignancy was considered in two cases, an appendiceal abscess in one, and a perforated viscus in another. The presence of two patients dying of miliary tuberculosis in a small series is of interest.

Seven of the patients complained of back pain, and in three it radiated to the groin and the lower extremity. The pain was either intermittent or persistent in character and was relieved by postural changes in two patients. The severity varied from mild in the less extensive cases to a shocking intensity in patients in whom rupture occurred. Ileus following perforation occurred in two patients. The duration of symptoms in five patients examined post mortem was two years in one and varied from 24 days to four and three-quarter months in four others. This is in accord with Kampmeyer's findings.[5]

In two patients the diagnosis of calcified aortic abdominal aneurysm was made as an incidental observation. These individuals had few or no symptoms or physical findings to direct attention to the presence of the aneurysm, and the roentgenograms alone established the diagnosis.

The physical findings of importance were few, but when present were significant. An intra-abdominal mass was palpated in three patients, and in two of these an expansile pulsation was felt. Tenderness and muscle spasm were frequently encountered in the lumbar area and in the anterior abdominal wall in either the upper or lower quadrants or both. In one patient, the tenderness over the lumbosacral spine suggested osteomyelitis. In another patient the presence of an aneurysm was unrelated to her illness. The right side was affected as regarded both symptoms and physical findings in five cases, the left in three. The predominance of right-sided symptoms and signs was unusual because the cases reviewed from the literature indicated that the left side was more frequently involved.

Roentgenographic examination was the most fruitful of the laboratory procedures. Of the four cases in which the correct diagnosis had been established all were alive at the time of writing. In each the roentgenogram either made the diagnosis or confirmed the clinical impression. Of the five patients who died and were examined post mortem the diagnosis had not been made before death although roentgenologic examinations were available. A review of these roentgenograms revealed sufficient evidence to suggest the possibility of an abdominal aortic aneurysm in each.

Calcification in the dilated vascular wall was present in six patients and was the most frequent finding. The ages of the patients in this group varied from 56 to 76 years. Angulation of the ureter was present in two cases, and the kidney was displaced and rotated in one. A semi-opaque pulsating mass could be outlined roentgenologically in the eighth patient after artificial pneumoperitoneum was induced. A filling defect in the cardia of the stomach was observed on the films taken during a gastrointestinal examina-

tion of one patient. Vertebral erosion was subsequently noted on these films.

The serologic reaction was positive in two cases. In both, autopsy revealed the presence of vascular syphilis. A serologic reaction was not available in one patient who had no evidence of syphilis post mortem. Other laboratory procedures were of little help.

Summary

This review and the cases of aortic abdominal aneurysm presented here may focus attention on the importance of painstaking roentgenological examination in the diagnosis of this obscure malady. The most recent contribution has been made by intravenous urography. The importance of identification of vascular calcification must be stressed, because even a thin, small deposit may, by its location, lead to a proper diagnosis. Pneumoperitoneum was helpful in one case.

The importance of a carefully taken clinical history and a thorough physical examination is apparent. They furnish the fundamental criteria upon which the diagnosis is established, and indicate the proper roentgenologic procedures necessary to facilitate investigation.

I would like to thank Dr. B. S. Epstein and Dr. E. L. Shlevin for their help and encouragement.

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CASE REPORTS

PRIMARY SPLENIC NEUTROPENIA, WITH REPORT OF A CASE *

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About one year ago Wiseman and Doan [1] published a report of five cases of "a hitherto unrecognized cause of neutropenia resulting from a pathologically altered, physiologic function of the normal spleen." They labelled this disease "primary splenic neutropenia." They postulated the theory that the spleen has a selective destructive action on the various cellular components of the blood. For instance, in thrombocytopenia, this selective destructive function destroyed the thrombocytes at an abnormally high rate; in hemolytic jaundice the erythrocytes were selected for destruction, whereas in "primary splenic neutropenia" the neutrophiles were the victim of this selective action. In no instance was there any interference with hematopoiesis as was evidenced by a normal bone marrow. Proceeding on this theory splenectomy was performed on these patients with a complete and permanent cure of their disease.

The case we are about to report fulfilled the criteria set up by them, probably in a purer form, because, owing to their publication, it was recognized earlier, and the spleen was removed rather early in the course of the disease, on the advice of Dr. Charles A. Doan, who studied the slides of the blood and the bone marrow. Our case showed no secondary anemia of any consequence, no diminution in the platelets and no jaundice, which was evident in whole or in part in their cases, which had had a more prolonged illness.

Case Report

Mrs. G. G., aged 59, housewife, was admitted to the Jewish Hospital on November 9, 1942. She had been seen by one of us at her home four days before her admission to the hospital. At that time she complained of chills alternating with fever. Her temperature was slightly elevated, but the physical examination was essentially negative. She did not appear very ill and aspirin was prescribed for her. There being no improvement in her condition during the succeeding four days, she decided to enter the hospital.

Her past history revealed that 11 months before, she had been confined in another hospital, with a diagnosis of pneumonia. Her blood count at that time showed erythrocytes 4,970,000 per cu. mm., leukocytes 2,750, with 24 per cent polymorphonuclear neutrophiles. She was confined to her bed almost continuously for the next five months, but gradually was able to assume some, but not all of her household duties, at the time of the onset of her present illness.

On admission her temperature was 101.6° F., pulse 124, and respirations 30 per minute. There was no cough, and there were no other symptoms, excepting the

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chills and fever. The physical examination revealed the spleen to be slightly enlarged, being barely palpable on deep inspiration.

No superficial lymph glands could be felt. There were no other physical findings of importance at this time. Her blood count showed erythrocytes 4,700,000 per cu. mm., leukocytes 2,000, polymorphonuclear neutrophiles 50 per cent, lymphocytes 40 per cent, monocytes 10 per cent, hemoglobin 10.5 grams. This count was rechecked in two hours, and the leukocyte count had dropped to 1350. On the next day, November 10, 1942, the leukocyte count was repeated. It was then 1300, with essentially the same differential count as the day before. The reticulocytes numbered 1.7 per cent and the platelets 204,000. On this day she was given a transfusion of 250 c.c. of whole blood. Her symptoms and physical examination remained unchanged. Her maximum temperature was 101.6° F. on that day. The next day, November 11, she appeared to be more acutely ill, and that afternoon her temperature rose to 105.2° F. Her respirations were 40 per minute and her pulse 132. The physical examination showed some evidence of consolidation at the base of the right lung, which was confirmed by roentgen-ray film. The spleen was definitely enlarged and easily palpated.

Her blood count at this time showed erythrocytes 4,500,000 per cu. mm., and leukocytes 800 with polymorphonuclear neutrophiles forming only 36 per cent of the total.

A sternal puncture was done by Dr. Harold K. Moss and the aspirated marrow was submitted to Dr. Philip Wasserman, Laboratory Chief of the Jewish Hospital, and to Dr. Charles A. Doan of the Ohio State University, and both pronounced it essentially normal. There was apparently no defect in the blood forming mechanism. Despite the low leukocyte count she was given 5 grams of sulfadiazine intravenously, as it was felt that the pneumonia was responsible for the change in her condition. An additional 4 grams was given by mouth during the next 36 hours. There was a prompt drop in her temperature and a marked improvement in her general condition. The spleen diminished in size and was no longer palpable after a few days.

On November 12, 1942 her blood count showed erythrocytes 4,810,000 and leukocytes 1,500 per cu. mm. of which 45 per cent were neutrophiles. On the next day the erythrocytes numbered 5,120,000 per cu. mm., and the leukocytes 950 of which 32 per cent were neutrophiles.

Following this she was given no medication of any kind. Her general condition improved, as did her appetite. She stated that she felt better each succeeding day. During the next two weeks, however, her leukocyte count did not exceed 1,950 per cu. mm. It was as low as 750 per cu. mm. and several days in succession it did not exceed 800. During this time the neutrophiles reached an all time low of 9 per cent.

Suddenly, on November 25, 1942 she experienced a severe stabbing pain in the lower left chest, accompanied by a chill and a rise in temperature to 102° F. A distinct friction rub could be elicited and a roentgen-ray film confirmed the clinical diagnosis of pleurisy. This film also showed that the pneumonia in the right lower lobe had completely healed. With the onset of the pleurisy the spleen again became easily palpable. Her blood count at this time revealed erythrocytes 4,130,000 per cu. mm., and leukocytes 1,450, of which 30 per cent were neutrophiles. Coincident with her improvement from this attack of pleurisy her leukocyte count again dropped so that on November 29, 1942 it was 700 with the polymorphonuclears forming 32 per cent of the total. The spleen was no longer palpable.

Numerous platelet counts showed them always to be in excess of 200,000 per cu. mm.

We felt that a splenectomy was imperative and this was performed on December 12, 1942. Just before operation her blood count was as follows: Erythrocytes 3,790,-

000 per cu. mm., leukocytes 1,400, polymorphonuclears 22 per cent, lymphocytes 51 per cent, and monocytes 17 per cent.

The artery was clamped at 10:55 a.m., and a count taken immediately showed 7,550 leukocytes per cu. mm. At 1 p.m. there were 6,000 leukocytes per cu. mm. with 82 per cent polymorphonuclears. Two days later the leukocyte count had risen to 14,650 per cu. mm. with 87 per cent polymorphonuclears. Her recovery was uneventful and she was discharged from the hospital January 1, 1943. On the day of her discharge her count showed erythrocytes 3,710,000 per cu. mm., leukocytes 3,950, polymorphonuclears 59 per cent, platelets 486,010.

A count made on January 16, 1943 was as follows: Erythrocytes 4,630,000 per cu. mm., leukocytes 4,300, hemoglobin 10.9 grams, polymorphonuclears 55 per cent, lymphocytes 29 per cent, mononuclears 11 per cent, eosinophiles 3 per cent, basophiles 2 per cent.

The patient was seen last on April 3, 1943. She was feeling perfectly well, and was able to attend to most of her household duties. Her count on that day was as follows: Erythrocytes 6,320,000 per cu. mm., hemoglobin 10.8 gm., leukocytes 12,450, of which 76 per cent were neutrophiles. Her general condition was steadily improving.

The description of the spleen by Dr. Philip Wasserman is as follows:

Gross Description: Specimen consisted of a spleen that weighed 570 grams. The spleen measured approximately 15 by 11 by 9 cm. in diameter. The capsule was tense and purplish in color. On section tissue was coherent and purplish red in color. Malpighian bodies and trabeculae were poorly made out. There were no areas of infarction, defect formation or neoplasm.

Gross Diagnosis: Splenomegaly (570 grams).

Microscopic Report: Spleen. Three sections. All showed essentially the same picture. Malpighian bodies were about average in size but were more widely spaced than average. No appreciable abnormality was seen here. The central arterioles showed somewhat thickened walls and apparent slight hyaline change present. The pulp showed a picture of fibrosis with apparently overly prominent reticulum. Sinusoids in places were distinctly dilated and in many areas the lining cells of the sinusoids were bulbous, swollen and present in several layers. In many areas the detail of the sinusoids was not well made out. There was a rare large cell present in the sinusoid or attached to the wall that appeared to be phagocytic and that apparently enclosed a recognizable polymorphonuclear leukocyte or a red blood cell. No areas of hemorrhage or of infarction were seen.

Final Diagnosis: Splenomegaly with apparent fibrosis and reticulum proliferation (spleen of a case of splenic neutropenia.)

Before splenectomy the case we have presented showed a tendency to repeated infections, owing doubtless to the low white count, but particularly to the low polymorphonuclear count. Of interest also, was her response to sulfadiazine during her attack of pneumonia, although her total white count at that time was only 800 per cu. mm. Her prompt and complete recovery following the splenectomy was in striking contrast to the very slow convalescence and incomplete restoration of health following the attack of pneumonia 11 months before. When this paper was written the patient was in perfect health.

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SUBACUTE BACTERIAL ENDOCARDITIS; REPORT OF A CASE WITH APPARENT FAILURE OF SULFONAMIDE PROPHYLAXIS COMPLICATED BY MASSIVE HEMOPERITONEUM *

By DAVID H. CLEMENT, Captain, M.C., A.U.S., and WARREN R. MONTGOMERY, Captain, M.C., A.U.S.

THE bizarre and protean manifestations of subacute bacterial endocarditis have been well described by numerous competent observers in recent years.[1, 2, 3] Although the treatment of this condition at present remains very unsatisfactory, we have of late acquired a better understanding of its pathogenesis. For over three decades the importance of the *Streptococcus viridans* in the etiology of this syndrome has been known. It has also been realized that this organism is most commonly found in the upper air passages and about the teeth and gums. The causal relationship of the extraction of teeth to this disease, especially in the presence of caries and pyorrhea, has been stressed by a number of writers, not only in the field of internal medicine but also by bacteriologists and dentists. Indeed, it is perhaps unfortunate that a greater number of internists are not more conversant with the numerous excellent papers on this subject which have appeared in the dental literature.

In the case of a patient with valvular or congenital heart disease suffering from pyorrhea or dental caries, or both, the physician is faced with an extremely difficult decision. He finds himself between the Scylla of leaving the focus alone and permitting it to grow worse and further menace the health of the patient on the one hand, and the Charybdis of extracting the infected teeth with the resulting hazard of having bacteria thus dislodged into the bloodstream settle on the deformed structures of the heart on the other. This dilemma is only intensified if the patient is suffering from active rheumatic fever which has shown no tendency to subside over several months. Under such conditions it would seem possible that the streptococcal focus in the teeth might even be etiologically significant in continuing the rheumatic activity. At least it would be reasonable to hope that if the focus could be removed without complications the patient would be in a better position than before.

For some years, many writers in medical and dental journals have stressed the fact that the extraction of carious teeth frequently is the precipitating event in the pathogenesis of subacute bacterial endocarditis. Only relatively recently, however, has another aspect of the problem been emphasized: namely, that individuals suffering from dental caries with or without pyorrhea are prone to have transient bacteremias spontaneously, whether or not their teeth are treated. In fact it is probable that a number of cases of subacute bacterial endocarditis which have been recognized shortly after tooth extraction were in fact already established at the time of the extraction because of preoperative spontaneous bacteremias.

The classic work of the English bacteriologists Okell and Elliott [4] is now well known. These investigators took blood cultures both before and after tooth

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extraction in 138 patients. The incidence of positive cultures after the extractions was found to vary from 34 to 75 per cent, roughly paralleling the severity of the caries and pyorrhea and the number of teeth removed. It is very significant, however, that in 110 of these patients who had appreciable pyorrheal disease, 12 or 10.9 per cent were found to have had positive blood cultures at the time of the examination, before any surgical procedures were undertaken. Surely no more convincing proof is needed to show that patients with infected mouths do suffer at least transient spontaneous bacteremias. In patients with cardiac deformities, the hazards from the standpoint of bacterial endocarditis are perfectly obvious. Merely to leave such mouths alone is to subject the patient to repeated insults which may well lead to disaster. Feldman and Trace [5] several years ago, in discussing the problem of bacterial endocarditis following the removal of teeth or tonsils, described a patient of theirs who had refused to have his infected teeth extracted. Three weeks later, however, with his teeth still untouched, the patient developed low-grade fever, abdominal pain, melena, splenomegaly, positive blood cultures and the classical picture of subacute bacterial endocarditis. They conclude: "Had his teeth been removed, we would have ascribed the endocarditis in this case to the operative procedure. Is it not conceivable that the infection may already be present in some cases when foci of infection are removed?" Libman, in writing on this subject, has expressed the same view.

With the advent of sulfonamide chemotherapy, it was naturally hoped that the situation in subacute bacterial endocarditis might be ameliorated, both from the standpoint of therapy and prophylaxis. As for the former, we have met with great disappointment. From the end of prevention, however, the outlook is brighter. Early in the development of sulfonamide therapy, it was shown [6] that *Streptococcus viridans* is generally inhibited in its growth when cultured in beef infusion broth containing sulfanilamide in a concentration of 10 mg. per cent. It soon became evident that in patients suffering from subacute bacterial endocarditis with persistent *Streptococcus viridans* bacteremia it was possible to sterilize the blood stream for varying periods of time by the administration of sulfanilamide, although the essential course of the disease generally was unaltered.[7] That some strains of *Streptococcus viridans* were more susceptible than others to sulfonamide therapy has been stressed by various investigators.[6, 8] Such observations naturally make the use of these drugs seem very reasonable from the prophylactic standpoint, even though in fact from a therapeutic angle they remain unsatisfactory in destroying bacteria once they are buried in a vegetation.

In 1940, Hageman [9] suggested the prophylactic use of sulfanilamide in patients with valvular heart disease who were to have dental extractions. He laid down no definite plan of attack. In 1941 Clagett and Smith [10] reported a definite routine for such patients, recommending hospitalization whenever possible, giving the drug (sulfapyridine then) until a blood level of 6 mg. per cent had been obtained, extracting offending teeth, and stopping the drug only after the socket was adequately healed. This regimen they recommended for patients with a history of heart disease or physical signs of heart disease (type not specified). The ultimate proper evaluation of such a program will take time. Its logic cannot be denied.

Looking at this disease from another direction, we have been much impressed by the variety of mechanisms which work to destroy the patient. General toxemia and anemia are almost invariably present. Embolic phenomena occur sooner or later in most cases, and their failure to suppurate has been commented upon by many observers. But the importance of the mycotic aneurysm in this disease is the feature we should like to discuss briefly. Although there is some debate as to the mechanism by which such aneurysms are formed, there is no longer any doubt that they are not rare in subacute bacterial endocarditis and that their rupture may be very significant clinically. The arterial wall is perhaps infected most often by bacteria in the blood stream lodging in it by way of the vasa vasorum, though infection through the intima is another possibility. In many instances, these mycotic aneurysms first make themselves known at autopsy.[1] On the other hand, rupture of mycotic aneurysms in this disease may be the cause of sudden death. When this occurs, the disaster results more often from the location of the hemorrhage than its amount. In other words the patient is more seriously threatened from the fact that the hemorrhage takes place in a vital area (e.g., brain) than from exsanguination.

In reviewing the literature, we have not found a case reported in which massive hemoperitoneum occurred. Because we recently had under our care a patient who suffered from such a condition, because it was puzzling to us at the time and yet was fortunately treated successfully, we report our experience in the hope that it will perhaps help others in the diagnosis and management of these very difficult patients. At the time our patient developed this complication we were confronted with the combination of active rheumatic fever with rheumatic heart disease, severe epigastric pain, hepatomegaly and splenomegaly, marked anemia which failed to respond adequately to repeated transfusions in quick succession, increasing abdominal distention with ileus and signs of peritoneal irritation, absence of blood in the stools, and the presence of marked leukocytosis. Medical, surgical and cardiac consultants could not make the diagnosis or agree on the advisability of surgical intervention. Indeed even after laparotomy, the true nature of the lesion was not fully appreciated.

In addition to the foregoing unusual and challenging episode (from which the patient recovered only to die one month later of a cerebral hemorrhage), we record our experience because it is an example of an apparent failure of sulfadiazine therapy before, during and after tooth extraction to prevent the development of subacute bacterial endocarditis in a patient with rheumatic heart disease.

Case Report

This child (D. B., born February 19, 1931; died May 31, 1942, Children's Hospital File Number 35866) was seen in the Out-Patient Department of The Children's Hospital at least yearly from the age of two years and five months until the time of his death at age 11 years and three months. Generally he made several clinic visits each year so that a fairly complete record of his progress is available.

At the time of his first visit (age: 2 years 5 months), it was learned that his birth and family histories were not remarkable. The past history revealed that he had suffered from frequent attacks of tonsillitis, otitis media, and cervical adenitis. Because of this history and the presence of large, chronically infected tonsils, the Ear, Nose and Throat Service recommended that his tonsils and adenoids be removed and

this was done shortly thereafter. During the next two years the child showed a normal weight gain and was well with the exception of mild upper respiratory infections. In March 1935, when four years old, the child was seen for a routine examination at which time a history of migratory joint pains for one month with fever was elicited. When seen he was symptom-free. The only positive physical findings were mild cervical adenopathy and a systolic murmur which was maximal over the pulmonic area. Thereafter he did well, showing normal weight gain, and frequent examinations of the heart clinically and roentgenographically revealed no significant abnormalities.

Because a heart murmur was noticed when the patient was hospitalized for excision of a fibroma of the right thigh in June 1941 (age: 10 years), he was seen by the Cardiac Service. Their findings included apparent enlargement of the heart to the left (not confirmed by roentgenogram), and a loud, 3–4 plus, high-pitched diastolic murmur of aortic quality over the entire precordium, heard best at the aortic area. Blood pressure was 115 mm. Hg systolic, with no diastolic reading obtainable. The electrocardiogram was within normal limits. Their diagnosis was aortic insufficiency, Class I. It is noteworthy that the child had maintained a normal weight curve up to this time, but thereafter showed a gradual downward trend as long as he lived. During the next six months repeated examinations revealed no new findings. In December 1941, the corrected erythrocyte sedimentation rate (Wintrobe) was normal, although the hematocrit was 37 per cent and the hemoglobin 13.2 grams.

In January 1942 (age: 10 years 11 months) this boy was admitted to the hospital with active rheumatic fever characterized by general malaise, pallor, fever, right ankle pain of one week's duration, and a corrected sedimentation rate of 12 millimeters at one hour. Within one week he was symptom-free and was discharged to the hospital's convalescent home where he was seen weekly by one of us.

On February 4, 1942, shortly after admission to the Convalescent Home, the patient complained of toothache. Signs of a periapical abscess of the first deciduous upper left molar were found. Root canal drainage was instituted February 5, 1942. Extraction at this time was deemed inadvisable because of the acute nature of the infection. Although the inflammatory process gradually subsided, the child continued to run a low-grade fever for the next two and one half weeks. At the end of this time he appeared to have received maximum benefit from the drainage. Since the fever persisted, however, it was felt that the remaining focus represented a serious menace to his rheumatic state. In order to break a vicious cycle, extraction of the tooth was thought justifiable, provided that it was done only after the patient had been adequately saturated with sulfonamide.

With this in mind, the patient was readmitted to the hospital for tooth extraction. On February 25, 1942 the diseased tooth was extracted as well as the adjacent molar which also appeared to be involved in the infectious process. For three days before and three days after dental surgery he received four grams of sulfadiazine daily. Although sulfadiazine blood levels were not obtained on this admission, it is to be noted that on the day surgery was performed, crystals of the drug were present in the urine in abundance. Furthermore the patient received the conventional full dosage of one grain per pound of body weight every 24 hours.

During this admission he ran a low-grade fever, reaching 101° F. rectally almost daily. The pulse rate averaged 100. Repeated examinations of the heart during his stay revealed no changes from those already noted. A blood culture (with paraminobenzoic acid) taken five days after the oral surgery, was sterile. Also at this time, the corrected sedimentation rate (Wintrobe) was 10 millimeters at one hour, the hematocrit was 27 per cent and the hemoglobin was 12 grams. The patient was returned to the Convalescent Home on March 6, 1942.

Here the boy appeared essentially unchanged for about 10 days. On March 15,

1942, 18 days after tooth extraction, he had a sudden rise in temperature to 103° F. by mouth and several small erythematous lesions appeared on his arms and legs. There were no subjective complaints. During the following week his temperature gradually returned to normal where it remained for 10 days.

Early in April the patient complained of pains in his hands, hips, and feet. Fever returned. On April 9, 1942, five weeks after tooth extraction the spleen was felt 3 centimeters below the costal margin for the first time. No evidences of embolic phenomena were discernible at this time. Examination of the heart, however, revealed apical systolic and diastolic murmurs which had not previously been present. On April 23, 1942 the patient began to complain of epigastric discomfort. The only new finding on physical examination was the fact that the liver edge was 3 centimeters below the costal margin. During the next four days, the child, although essentially afebrile, showed a rising pulse rate. The epigastric pain grew progressively more severe. On April 27, 1942 he complained of very severe abdominal pain and fainted for a brief interval. He was again readmitted to The Children's Hospital.

Admission examination disclosed an acutely ill, pale child complaining of marked abdominal pain. The temperature was 98° F., pulse 130, respirations 20 and blood pressure 130 mm. Hg systolic, no diastolic reading obtainable. The skin was clear. The mouth appeared to be in good condition, though there was marked pallor of the mucous membranes. The lungs were not remarkable. The cardiac findings were essentially as previously described, i.e., double mitral and aortic murmurs. The abdomen was strikingly distended and peristalsis could not be heard. There was tenderness in both upper quadrants, more on the left, with definite rebound tenderness throughout the entire abdomen. The upper abdominal pain was aggravated by deep inspiration. No fluid wave was demonstrable, and liver and spleen were not felt, though distention and tenderness made examination unsatisfactory. Rectal examination revealed some fullness and tenderness anteriorly but no definite masses were made out. The stool was normal in appearance. Reflexes were physiological at this time. Laboratory findings revealed a profound anemia: Hemoglobin 7.5 grams; red blood cells 2,900,000 with a hematocrit of 21 per cent. A marked leukocytosis of 48,300 was accompanied by a differential white cell count showing a moderate shift to the left. Urinalysis was normal. The blood non-protein nitrogen was 36.4 mg. per cent. Roentgenographic examination of the chest revealed clear lung fields and a cardiac silhouette showing some preponderance of the left ventricle but with no actual enlargement of the heart.

During the next three days the patient remained in a precarious condition. Because of clinical and laboratory evidences of blood loss, he received three transfusions totaling 950 c.c. of whole blood during this time. In spite of transient rises following transfusions, the red count and hemoglobin remained at critical levels, and the hematocrit fell steadily to 16 per cent. On the third day there was still a significant leukocytosis of 33,400. Daily measurements of the abdominal circumference revealed progressive enlargement. Audible peristalsis remained absent and on the third day a fluid wave and shifting dullness could be demonstrated. Repeated examinations of the stool for occult blood were negative.

On the second day a surgical consultant, admitting an intra-abdominal vascular accident most probable, felt that since there was no blood in the stools, there had been no interference with the intestinal blood supply and he favored a diagnosis of splenic infarction with hemorrhage. In view of the patient's condition, he recommended conservative therapy. On the same day the patient was seen by a cardiac consultant whose opinion was that a hemorrhage into the peritoneal cavity had occurred and that laparotomy should be performed within 24 hours if the condition of the patient failed to improve. Because in the following two days the child grew gradually worse, evidence of blood loss continued, and abdominal distention and ileus persisted, all consultants agreed that laparotomy was the only recourse.

Operation was performed on April 30, 1942. Under nitrous oxide, oxygen, and ether anesthesia, and with a transfusion of whole blood running, the abdomen was opened through a left rectus incision in the upper third of the abdomen. The peritoneum was under tension. The peritoneal cavity was found to be completely filled with clotted blood which was removed. Examination of the small bowel disclosed a dusky loop about 15 cm. long in the upper portion of the jejunum. The impairment of circulation here seemed to be due to a thrombotic process which had started about 5 cm. distal to the root of the mesentery in this area. Hemorrhage had taken place between the two layers of the mesentery beyond this point, distending them with a large clot about 8 cm. square and 2 to 3 cm. in thickness. One layer of the mesentery had previously ruptured, and through the opening blood could be seen oozing into the peritoneal cavity.

Several small radial incisions were made in the mesentery and through these the entire clot was evacuated. Approximately six bleeding points were then evident in the mesentery and sutures were placed for their control. Following the removal of the clot and ligation of the bleeding points, the bowel was seen to assume better color and no great impairment in its circulation could be observed. Further examination of the mesenteric vessels was omitted because of the patient's precarious condition, and the abdomen was closed without drainage. It is noteworthy that the true etiology of the hemorrhage was not established at the time of operation.

Postoperatively the patient's condition showed dramatic improvement. Response to transfusion was prompt and now brought significant rises in hemoglobin and hematocrit levels. The child continued to run a low-grade fever throughout his remaining month of life, with average daily rises to 101° F. There were no evident surgical sequelae. The wound healed normally. The abdomen resumed its normal contours, the appetite improved, and the bowels moved regularly. On the thirteenth postoperative day, the boy complained of pain in his left upper quadrant and the spleen was found enlarged and tender. Although previous blood cultures had been sterile, a culture taken on the fourteenth day postoperatively yielded *Streptococcus viridans,* 4 colonies per c.c. (Paraminobenzoic acid was added to the culture media.) Upon identification of this organism, sulfadiazine by mouth was started in dosage of 1 grain per pound body weight every 24 hours and so maintained until death. Nevertheless *Streptococcus viridans* was repeatedly isolated from subsequent cultures. A small petechial hemorrhage appeared on the tip of the nose on the twenty-eighth postoperative day.

On May 31, 1942, just one month after operation, the child suddenly developed a severe right frontal headache and flexion of the neck became painful. Three hours later projectile vomiting occurred and there were neurological signs of increasing intracranial pressure. Bizarre and profound reflex changes appeared terminally. Seven hours after the onset of his frontal headache he lapsed into coma, blood pressure rose, respirations became irregular and he died three hours later.

Postmortem examination was performed 11 hours after death by Dr. Kornel Terplan. An abstract of the autopsy protocol follows. Both lungs showed fairly recent passive hyperemia and slight hemosiderosis. There were scattered petechial hemorrhages in the visceral pleura and in the mucosa of the trachea and bronchi. The pericardial sac contained 15 c.c. of serous fluid (normal). The heart was considerably enlarged. It weighed 250 grams (normal: 122 grams).[11] The left ventricle was hypertrophied and dilated. The wall of the left ventricle measured 1.7 cm. in thickness (normal: 1.0–1.2 cm.); that of the right measured 0.3 cm. (normal). The circumference of the mitral valve was slightly increased and attached to its anterior leaflet was a soft friable vegetation about 3 by 4 by 2 mm. A few similar but minute, grayish-white vegetations were seen around the upper parts of the chordae tendineae of the anterior papillary muscle. The aortic leaflets were distinctly reduced in height and at the inner aspect of the right leaflet there was a coarse granular vege-

tation. The line of closure was definitely thickened. There were also a few friable vegetations attached to the left leaflet. The aorta was normal, as were the coronary arteries. In the posterior wall of the left ventricle there was a nodular scar about 3 cm. in diameter. Scarring was also noted in the apices of the papillary muscles.

The abdominal cavity contained no free fluid. The site of previous hemorrhage in the mesentery was completely healed. There was distinct hemosiderotic discoloration of the peritoneum in this area. Several sutures remained around a third-order branch of the superior mesenteric artery, about 3 cm. proximal to the intestine. Just distal to these ligatures could be seen the remains of an old ruptured mycotic aneurysm. In a second-order branch of the superior mesenteric artery, was found a second, cherry-sized, mycotic aneurysm with definite hemorrhages in its wall. The entire intestinal tract was otherwise normal in appearance.

The spleen was greatly enlarged, weighing 400 grams (normal: 87 grams). There was a huge mycotic aneurysm of the splenic artery at the hilus of the spleen. This measured 2½ cm. in diameter. The cut surface of the spleen revealed almost confluent infarctions, some anemic and some hemorrhagic in an area 6 by 10 cm. in the central portion of the organ. The kidneys were markedly hyperemic and both of them showed scattered petechial hemorrhages and anemic infarctions throughout. Similar hemorrhages were noted in the mucosa of the bladder. The adrenals were not remarkable and the liver showed only slight edema on the cut surface.

On opening the cranium, the dura mater was found greatly distended. Extensive, recent, subarachnoid hemorrhage covered practically the whole right hemisphere and the base of the entire brain. An aneurysm measuring 3 mm. in diameter of a distal branch of the right middle cerebral artery was found within the leptomeninges. This had ruptured in the area of the foot of the third right frontal gyrus. Not only had blood extended into the subarachnoid space from this lesion, but there had been a massive hemorrhage into the substance of the brain extending into the ventricle. The area of the hematoma measured 11.5 cm. by 6 cm. and involved most of the white substance of the right cerebral hemisphere just above the lateral ventricle. All ventricles were filled with recently clotted blood. In addition, there was a recent aneurysm of the right posterior communicating artery, measuring 3 mm. in diameter.

Final pathologic diagnoses were: (1) Subacute bacterial endocarditis of the mitral and aortic valves with distinct insufficiency of both valves. (2) Embolic infarctions of the myocardium, old. (3) Mycotic aneurysms of two mesenteric arteries, of the splenic artery, of the distal branch of the right middle cerebral artery, and of the right posterior communicating artery. (4) Focal embolic glomerulonephritis.

Summary and Conclusions

We have reviewed the literature on certain aspects of subacute bacterial endocarditis and have reported a case. We feel that the following points are noteworthy:

1. Patients suffering from dental caries with or without pyorrhea are prone to suffer transient bacteremias with *Streptococcus viridans* and other organisms found about the teeth. These bacteremias occur spontaneously without the performance of oral surgical procedures, although tooth extractions in such patients have been shown conclusively to precipitate such seeding of the blood stream in a high per cent of cases. In patients with cardiac deformities (congenital or rheumatic), such insults may result in subacute bacterial endocarditis.

2. Given a patient with valvular or congenital heart disease with dental caries or pyorrhea, it would seem best to do three things in the following order: (*a*)

quickly establish adequate sulfonamide blood levels, preferably with sulfadiazine at present; (*b*) clean up the teeth and gums as much as possible by appropriate dental hygienic measures so as to minimize subsequent wound contamination; and (*c*) extract the carious teeth, preferably in stages. The drug should be maintained postoperatively until the sockets show evidence that clean healing has been well established. Should the patient in addition be suffering from active rheumatic fever, the regimen might be deferred temporarily to allow the rheumatism to subside. If this failed to occur after a reasonable interval, the above program could justifiably be started, with the full realization, however, that the rheumatic process might be aggravated temporarily by the sulfonamides.

3. A policy of watchful waiting is not reasonable in these patients with structural heart defects and dental caries for the reason that if left alone, the caries becomes worse and transient bacteremias will occur even though the teeth are not touched. Occasionally such patients have been subjected to dental surgery after a bacterial endocarditis has been established (though not recognized) and the tooth extraction has been erroneously regarded as the cause of the disease.

4. Mycotic aneurysms in bacterial endocarditis may rupture and lead to a very large hemorrhage, producing circulatory collapse, shock, profound anemia, i.e., the clinical picture of severe blood loss. When such a hemorrhage occurs in the peritoneal cavity, the circulatory picture may be further complicated by ileus, abdominal distention, signs of peritoneal irritation and marked leukocytosis. Clinically the syndrome may simulate peritonitis, or mesenteric thrombosis or embolism.

5. A case has been reported which illustrates the foregoing points. Adequate sulfonamide therapy for three days before and three days after tooth extraction failed to prevent the occurrence of subacute bacterial endocarditis. (That the bacterial endocarditis had not already been established before the teeth were extracted cannot be conclusively proved. Clinically this seems improbable.) In the course of this illness, the patient developed a massive hemoperitoneum (not previously reported in the literature). The true cause of the hemorrhage (ruptured mycotic aneurysm of the superior mesenteric artery) was not established even at the time of laparotomy, although the bleeding was successfully checked by suturing and the patient recovered, only to succumb a month later to massive cerebral hemorrhage, also from a ruptured mycotic aneurysm.

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TUBERCULOID LEPROSY: A CASE REPORT *

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At the present time, there seems to be a likelihood that we shall see more cases of leprosy in this country than ever before. It is important to be on the alert for such cases at all times and more so during these times of global warfare and travel. Contrary to what is commonly believed, this disease is not uncommon in the United States. Most of the cases have been seen in the Gulf Coast area, namely, Florida, Louisiana, and Texas, although sporadic examples of the disease have been reported from the whole country.[1, 2] There is a general misconception that this disease is seen only in tropical and semitropical climates. Sutton [2] states that the greatest number of cases in proportion to total population occur in Iceland. The disease is endemic in Mexico, Central and South America. Pardo-Castello and Tiant [3] find that all healthy persons in Cuba are lepromin positive. This, they believe, is because it is a leprous country and all have been in contact with leprous persons for many years.

I have only discussed the local prevalence of leprosy to demonstrate that it is not at all uncommon in our front yard. Its geographical distribution is such that our troops will undoubtedly be exposed to it to some extent and we may see an increasing number of cases in the coming years. It is hoped that the presentation of this case will stimulate a greater watchfulness for this disease.

Case Report

The patient, a 23 year old male of Japanese parentage, was admitted to the hospital on September 2, 1943 with the diagnosis of tinea circinata. He had noted a skin eruption on his buttocks seven months prior to admission. In the course of a month or two, the eruption had spread to his face, the lateral surface of his left thigh, right arm and forearm, and both hands and feet. It had been moderately pruritic for the first two months but was entirely asymptomatic after that. He had never noted any shooting pains, numbness or tingling in his extremities. He had had a watery nasal discharge when the weather was hot during the past year and a monthly nose bleed during this period. He had never been troubled by purulent nasal discharge.

The patient was born in Baldwin Park on the outskirts of Los Angeles. He had spent three months on one of the Hawaiian Islands in the summer of 1929 and had resided in Japan from 1930 to 1931. Up to the time of induction, 18 months before, he had been a truck gardener.

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His past medical history was entirely non-contributory.

His family history did not disclose the presence of any familial diseases. His father was living and well. His mother had died of causes unknown to the patient. One sister was living and well and a brother had died at the age of seven with an undiagnosed fever. The patient had been married for one year. His wife was delivered of a full term healthy infant while he was under observation. She was in good health. No history of any contact with persons suffering with a disease similar to his own could be elicited.

FIG. 1. Demonstrates thickening of features suggestive of the leonine facies. The lesions described in the eyebrows and in the zygomatic areas of the cheeks are clearly seen. Photo by U. S. Army Signal Corps.

On admission, the patient weighed 130 pounds and his height was given as 65 inches. The striking feature on examination was the presence of large areas of skin involvement with slightly raised arcuate and festooned borders enclosing areas of slightly thickened, scaling dry skin. The borders measured one to one and a half centimeters in width and consisted of reddish brown, flat-topped papules fused to form a continuous margin. The hairs were present in the involved areas. The smaller lesions were basically similar and consisted of slightly elevated plaques with branny scaling centrally. In the smaller lesions there were no central clear zones.

In general, the distribution of the skin lesions was symmetrical. There was a large area measuring 10 by 15 centimeters involving the adjacent areas of the two buttocks. This was the first lesion. There was a 23 by 30 centimeter figure on the lateral aspect of the left thigh and another 15 by 30 centimeters involving the dorsal and lateral surfaces of the right arm and forearm. There were smaller lesions varying from one to 10 centimeters in diameter scattered in the lateral portions of both

eyebrows; over the right zygomatic region; below the lobe of the right ear; under the right mandible; at the base of the neck posteriorly; on the palmar surfaces of the right thumb and third and fourth fingers; the right thenar and hypothenar eminences, the dorsum of the left hand; the palmar aspects of the left thumb, third and fifth fingers; the left elbow and the lateral aspect of the left arm; the right lateral malleolus and the area just proximal to it; the lateral border of the right foot and the medial surface of that heel; the lateral surface of the left leg and the dorsal surface of the left great toe. The larger areas of skin involvement were hypesthetic or anesthetic to pin prick.

FIG. 2. Illustrates the initial lesion noted on the buttocks. Photo by U. S. Army Signal Corps.

The ulnar and radial nerves were diffusely and uniformly thickened bilaterally to form trunks one centimeter in diameter. Three or four firm, freely movable glands were felt along the course of the thickened ulnar nerve trunk. There were no sensory changes in the areas supplied by these nerves. The right superficial auricular nerve was readily visualized by having the patient look over his left shoulder and was palpable and whipcord-like.

On admission the red blood cell count was 5,700,000 with a hemoglobin of 95 per cent (T) and a white blood cell count of 6350. The differential blood count was polymorphonuclears 58 per cent, lymphocytes 38 per cent, and eosinophiles 4 per cent. The sedimentation rate (Cutler) was 1 millimeter and 2½ millimeters per hour respectively. The blood Kahn and Wassermann reactions were negative, and the serum total cholesterol was 148.2 milligrams per cent. Urine examination showed no abnormalities. Nasal scrapings and ear lobe preparations failed to demonstrate

acid-fast organisms. Skin scrapings revealed no fungi. Roentgenogram of chest was reported as negative and roentgenograms of the hands showed no lesions suggestive of sarcoidosis. Skin tests done with 0.2 c.c. of 1 to 10,000 histamine hydrochloride resulted in a 3 centimeter wheal but no zone of erythema in the anesthetic area of the buttock. A similar wheal surrounded by a 0.5 centimeter border of erythema developed when the test was performed just outside the anesthetic area.

A biopsy was taken from the margin of the lesion on the buttocks. The microscopic report was as follows: "There are many small areas of chronic granulomatous inflammation lying in the dermis and extending along the skin appendages into the

FIG. 3. Illustrates the lesion described on the lateral aspect of the left thigh. Photo by U. S. Army Signal Corps.

subcutaneous fat. Some of these granulomatous lesions incorporate peripheral nerves. The most striking features of the lesions are the giant cells. The other cells are occasionally epithelioid but many lymphocytes are likewise present. Some of the epithelioid cells are vacuolated and some have almost clear cytoplasm. There is no instance of necrosis. Acid-fast stains controlled by positive tuberculous material and others very lightly decolorized failed to demonstrate acid-fast bacilli. No other causative agent is found. Neither tuberculosis nor leprosy can be excluded."

Another biopsy was taken of the enlarged epitrochlear glands. The microscopic description follows: "The lymph node structure is preserved but there is much desquamation of lining cells into the lymph sinuses and mixed with these cells are small numbers of lymphocytes and leukocytes. Although occasional pale cells are seen

these do not resemble the large globular cells of leprosy. The type of alteration in the lymph node is that commonly designated as reactive or sinus catarrh."

The Army Medical Museum reviewed the sections and gave the following report. "It is our impression that the lesion is leprosy of the tuberculoid type. This is a form of leprosy in which the organisms frequently are not found in the histologic sections."

During the period of observation, the patient remained asymptomatic and there was no evidence of spread or regression of any of his lesions. A complete examination of the eye and its appendages revealed no findings except enlargement of the corneal nerve fibrils on slit lamp study.

Discussion

The diagnosis of leprosy was suspected on the day of admission. Tinea circinata and tuberculids were considered in the differential diagnosis. The presence of the anesthetic skin lesions and the thickened nerve trunks fulfill the criteria of the United States Public Health Service for the diagnosis of leprosy.[2] Manson-Bahr [4] states that leprosy is the only skin disease showing anesthesia. The sedimentation rate was extremely slow. This confirms Manson-Bahr's [4] statement that the sedimentation rate is always decreased in leprosy. The histamine skin test has been suggested by Pardo-Castello and Tiant [3] in determining the state of the nerve supply to the involved areas in patients, especially children, who cannot coöperate in the thermal and pin prick tests necessary. When a solution of histamine is injected into the normal skin a small wheal surrounded by a halo of erythema results. The wheal is due to local action of the histamine on the capillary walls and the erythema is the result of an "axon reflex." When the local nerve endings are destroyed or if the peripheral nerves supplying the area are damaged, the "axon reflex" action is knocked out. Hence, as in our case, the area of erythema was absent when the histamine was injected into the anesthetic area on the buttocks.

Pardo-Castello and Tiant [3] recently presented the South American classification of leprosy into lepromatous, tuberculoid and non-specific types. This classification appeals to me because it is at the same time clinical, pathological and physiological, in contradistinction to the older purely clinical classifications. Furthermore, when cases are classified in this manner, fairly accurate prognostication is made possible.

Our case was classified as tuberculoid before the final biopsy report was returned because of the presence of the characteristic skin lesions described by Pardo-Castello and Tiant [3] as "sharply circumscribed erythematous patches or flat infiltrations, often ring shaped or festooned, with macular centers and elevated border, the latter being uniform or composed of small nodules arranged side by side"; the typical pencil-like enlargements of the nerves; the tuberculoid structure described in the first biopsy report and the failure to demonstrate the lepra bacilli. In the older classifications this case may be labeled either as anesthetic or mixed leprosy. In tuberculoid leprosy, the prognosis is good; the patient's immunity is high, he does not excrete bacilli and is, therefore, not dangerous to the community.

SUMMARY

A case of tuberculoid leprosy is presented. The importance of being on the lookout for this disease as our soldiers return from the far flung corners of the earth is emphasized. A plea is made for the adoption of the South American classification of leprosy.

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BLEEDING PEPTIC ULCER IN A YOUNG AVIATION CADET: REPORT OF CASE *

By MAURICE B. SIEGEL, 1st Lt., M.C., and BERGEIN M. OVERHOLT, Capt., M.C., A. U. S., F.A.C.P.

INTRODUCTION

THE concept of peptic ulcer as a psychosomatic disease is rapidly gaining ground,[1, 2] and apparently with good reason, as the increased abnormal psychic stimuli created by the advent of the war and the need for adjustment to a new environment are all reflected in the many reports of an appreciable increase in the incidence of dyspepsia and ulcer syndrome. Numerous reports from geographically scattered Army General Hospitals [3, 4] show a 30 to 35 per cent incidence of proved peptic ulcers in admissions to the Gastrointestinal Services of these hospitals. Hurst,[5] in his survey of digestive disorders in the English and French armies, found that whereas gastric disorders were comparatively rare in World War I, the symptom complex of dyspepsia presents the largest single type of disease in the modern army. Similar experiences were found in the Royal Navy,[6] Royal Air Force, and Canadian Army.[7]

We present our case for several reasons. *First:* after a survey of the literature, this appears to be the first case of a bleeding duodenal ulcer in an aviation cadet who was actively engaged in routine training, including acrobatic spins, rolls, and dives.

Second: to present several interesting features in this case; (a) the patient had no symptoms while flying, but only felt weak and faint while walking to and from his plane, carrying his parachute pack which weighed approximately 50 pounds, (b) to correlate his flying record as noted by his instructor with the progression of his anemia.

Third: hemorrhage from a duodenal ulcer in a patient 19 years old is not a very frequent occurrence.

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Case Report

An aviation cadet, age 19, was admitted to the Station Hospital on January 16, 1943 from a nearby primary air force school, for observation and treatment of weakness and pallor, evident for a few days prior to admission.

He stated that for about 10 days preceding his entry into the hospital he felt weak and tired easily, a most unusual situation for him. On January 9 he took a cathartic because he had vague upper abdominal distress, and late that day he had an abrupt bowel movement which was "coal black." He felt faint, dizzy, and perspired freely, but shortly afterwards regained his equilibrium and was able to go back to his studies in the evening. He continued to notice black stools until January 15. During the entire time that he was bleeding, he continued to fly because he desired to graduate with his primary class some 10 days later. On January 11, his friends and associates noticed his pallor; he began to feel weak and listless, tire easily, and barely manage to get to and from the cockpit of his plane, wearing his flying suit and parachute. For three days prior to his admission to the hospital, he was actively engaged in practicing solo acrobatics, such as snap rolls, loops, slow rolls, spins and dives, and at no time during these maneuvers in the air did he experience "black-outs," scotomata, dyspnea, or even feel faint. On January 13 he felt so weak that he fell to the floor upon arising from his bed, and reported to sick call for observation. Two days later he entered this hospital.

On admission we saw a well-developed and well-nourished young white adult male with marked pallor, all the more striking because of his fair complexion making him look almost cadaverous. He was very definite upon questioning that he did not at any time have abdominal pain, other than the slight discomfort experienced on the

Table I

Date	Hb (gm.)	RBC	Occult Blood
1/16/43	33.2% (5.25 gm.)	2,000,000	4+
1/19/43	37% (5.75 gm.)	2,500,000	3+
1/20–24/43	40% (6.3 gm.)	2,500,000	1+
1/26/43	48% (7.55 gm.)	2,900,000	Negative
	(ferrous sulfate added to diet at this time)		
2/2/43	59.6% (9.25 gm.)	3,110,000	Negative
2/8/43	74.5% (11.55 gm.)	3,600,000	Negative
2/15/43	93% (14.45 gm.)	4,500,000	Negative

(Hemoglobin determined by photo-electric cell after the method of Peters and Van Slyke, wherein 100 per cent is equivalent to 15.5 gm. Hb)

first day that he noticed tarry stools. Physical examination revealed marked pallor of the skin, mucous membranes and nail beds, a hemic systolic murmur, and tachycardia of 100 per minute. Blood pressure was 100 mm. Hg systolic and 65 mm. diastolic, and the patient stated that he felt faint, dizzy and weak. Laboratory studies showed a hemoglobin of 33 per cent (5.2 gm.) and a red blood cell count of 2,000,000. Stool examination showed a 4+ reaction for occult blood. Bleeding and clotting time, platelet count, leukocyte count, differential, and urine examination were entirely normal. The patient was regarded as having a silent bleeding ulcer and started on a modified Sippy routine supplemented with colloidal aluminum hydroxide and tincture of belladonna. On this régime he showed rapid improvement, and as his stools became negative for occult blood, his hemoglobin and erythrocyte count correspondingly rose (table 1).

He was confined to his bed for six weeks, and at no time did he exhibit abdominal pain, except in the latter days of his stay in the hospital, when, if he did

not get his milk on time or if it did not contain adequate cream, he would have mild epigastric discomfort, promptly relieved by intake of milk and cream. A gastrointestinal series was performed when all evidence of bleeding had ceased and a deformed, irritable, poorly-filled spastic duodenal bulb was demonstrated. After the stools had become negative for occult blood, ferrous sulfate was given in 5 gr. doses three times a day because the rate of rise of his red blood cell count and hemoglobin had slowed down considerably. Following the institution of iron therapy his hemoglobin promptly rose to 90 per cent and his red blood cell count to 4,500,000.

Discussion

One can speculate as to whether the life of an aviation cadet, with its particular stresses and strains, was the main causative factor in this bleeding episode, and, if so, whether he should be allowed to resume his flying career. The problem of ulcer in the Army differs from that in civil life in that the trend today is to discharge these ulcer cases because in the long run they are more of a burden to the service and hence are better off under conditions of civil life where dietotherapy can be more carefully followed and attempts can be made at modifying those adverse conditions of stress and strain to which the patient might be subjected.

A rather interesting sidelight on the case has already been briefly mentioned in that this patient with an erythrocyte count of 2,000,000 and a hemoglobin of 32 per cent was able to fly and do acrobatics and not show any dyspnea or anoxia, such as might have been expected with the arterial oxygen saturation so low. The arterial blood of a patient whose hemoglobin is 30 per cent of the normal value will contain only a little over six volumes per cent of oxygen,[8] and hence, in order to compensate the circulation rate (cardiac output) is increased, each unit of blood giving up a smaller part of its oxygen load than normal to the tissues, so that the venous blood has the same relative percentage of oxygenation as normally. It would appear that physiologically he had adjusted to his new low blood level and was able to carry on his flying activities. However, his proficiency as gauged by his flight instructor was markedly impaired and he was given three consecutive unsatisfactory check flights, something that had not happened previously at any time during his training period. They stated that he showed improper coördination, poor judgment and increased tenseness during those flights while he was bleeding actively. Previous to that time he had received average satisfactory ratings for his flights.

Summary

1. We have presented a case of bleeding peptic ulcer in a young air cadet actively engaged in routine flight training. To our knowledge this is the first such case to be reported in the literature.

2. The ability of the patient to continue to fly in spite of a rather profound anemia has been stressed, although it would appear that his flying efficiency was impaired in proportion to the degree of anemia.

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CARCINOMA OF THE UMBILICUS METASTATIC FROM CARCINOMA OF THE STOMACH *

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CARCINOMA of the umbilicus, either primary or occurring by metastasis has seldom been reported, but has long been known to occur. Osler,[1] in the first edition of his textbook, speaking of cancer of the stomach, stated: ". . . Occasionally, a secondary metastatic growth occurs subcutaneously, either at the navel or beneath the skin in the vicinity. In an instance recently under observation in a patient with jaundice, which developed somewhat suddenly and was believed to be catarrhal, there were no signs of enlargement of the liver or tumor of the stomach, but a nodular body developed at the navel, which on removal proved to be typical scirrhous carcinoma. A second case in the ward at the same time, with an obscure doubtful tumor in the left hypochondria, developed a painful nodular subcutaneous growth midway between the navel and the left margin of the ribs." Alvarez [2] also called attention to examination of the umbilicus for metastasis from gastric cancer, and recently Walters, Gray and Priestly,[3] referring to carcinoma of the stomach, stated: "In an occasional case, a metastatic nodule may be palpated or even seen in the umbilicus. When present, this nodule is characteristic of carcinoma and can hardly be mistaken for any other type of lesion. The umbilicus may be discolored a dusky bluish red (figure 31)." The condition, however, is evidently quite rare and recently Alvarez [4] has written us as follows: "I am sure that obvious metastasis to the umbilicus is rare. I remember seeing only one striking case in years. As I remember, in that case, the man had a tumor around the navel as big as a doorknob before he had any symptoms of indigestion." (Dec. 21, 1942.) Metastasis to the umbilicus in cases of carcinoma of the stomach is thus apparently a rather uncommon finding, but when a tumor mass does occur there, it should be suspected to be secondary to malignancy within the abdomen and especially in the stomach. Primary cancer of the umbilicus is by far more uncommon than is the metastatic form.

Cullen,[5] in his monograph on the umbilicus, a large and exhaustive treatise, collected 27 cases of carcinoma of the umbilicus secondary to carcinoma of the

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stomach, including one of his own. It is our impression that he thoroughly reviewed the medical literature up to that time. Warner [6] reported an additional case in a man aged 54 together with a case of carcinoma of the rectum with metastasis to the umbilicus. Witthauer [7] reported six cases of carcinoma of the stomach in which metastasis to the umbilicus was present. The ages were 17 (!), 23 (!), 27 (!), 41, 48 and 61 years. The umbilicus was frequently blue-red or bluish in color and in some, merely a hard tumor was felt. In some instances Witthauer believed that carcinomatous emboli into persistent paraumbilical veins took place; in others, direct local extension through the peritoneum to the subcutaneous tissue of the umbilicus probably occurred and in others the mode of extension was apparently by metastasis through lymphatic and blood vessels. In one case, a man aged 41, only in the umbilicus was there any evidence of metastasis, even upon operative exploration. He lived nearly a year following partial gastrectomy before dying as a result of metastasis. Hartmann [8] reported one case of carcinoma of the umbilicus in a man, secondary to carcinoma of the stomach. The lesion had a raised border, was slightly ulcerated in the center and was of hard consistency. It proved to be adenocarcinoma upon microscopic examination. Including Osler's [1] case and the one illustrated in Walters, Gray and Priestly's text,[3] there have been 37 cases of carcinoma of the umbilicus metastatic from cancer of the stomach reported. We wish to report one additional case.

Case Report

A white woman, aged 44, was first seen by one of us (L. E. L.) on September 21, 1942 and was admitted to St. Mary's Hospital. Her past history was unimportant. She was extremely nervous and complained of migratory pains in the back and neck. For about a year prior to her admittance to St. Mary's Hospital, she had a gradual loss of appetite, mild pains in the epigastrium, gaseous distention of the stomach and occasional nausea after meals. She had lost weight progressively. She had been examined in a hospital in California in April, 1942 where a diagnosis of peptic ulcer of the stomach had been made. She was treated medically and improved considerably. Roentgenographic examinations were made in California in June, and she was told that there was a marked improvement in her condition. About this time she began to notice a peculiar hardness of the umbilicus which gradually became rather tender. Her nervousness increased and vague pains developed in her back and neck.

The physical examination revealed a poorly nourished woman who was extremely nervous and complained of fleeting pains through her back and neck. There was slight tenderness in the occipital region extending down into the posterior cervical region. The eyes were normal and the ears, nose and throat were not remarkable. There was no adenopathy or rigidity of the neck, although there was some muscle spasm on pressure over the posterior cervical area. The chest was symmetrical, expansion was equal, voice and breath sounds were normal, and there were no râles. The breasts were slightly atrophic and pendulous but showed no masses. The apex beat of the heart was palpable in the left fifth interspace; the sounds were regular and rhythmic with no murmurs. The abdomen was scaphoid and showed no rigidity. There was some tenderness in the right hypochondrium extending down into the right lower quadrant. There was a suspicious mass in the upper abdomen which was moveable and felt rather hard. The umbilicus presented a granular-frosted-appearing induration about 2.5 cm. in diameter. There was also an area

of induration around the navel apparently beneath the skin approximately 2 cm. beyond the umbilicus. The genitalia were normal. The pelvic examination revealed a small freely moveable anteflexed uterus. The adnexa were normal on palpation. The upper and lower extremities showed no atrophy or edema.

The blood count showed: hemoglobin, 100 per cent (14.5 gm. Hb); erythrocytes, 5.05 millions; leukocytes, 5,200 per cu. mm.; neutrophiles, 69 per cent (one non-filament); lymphocytes, 26 per cent; eosinophiles, 2 per cent; basophiles, 3 per cent. A specimen of urine was normal except for a faint trace of albumin. The Kolmer Wassermann, and Kahn reactions on the blood serum were negative.

Roentgenographic examination showed no disease in the heart and lungs. No cardiospasm or signs of gastric retention were found but there was a suggestion of a small ulcer on the lesser curvature of the stomach about two inches (5 cm.) above the pylorus. The stomach and duodenum were very irritable and the roentgenologist (Moreton J. Thorpe, M.D.) stated: "It is possible that the extreme nervousness (of the patient) is responsible for all the duodenal and gastric irritability; but also there is a very strong suspicion of a gastric ulcer. If the patient could be quieted down, reëxamination might be warranted." Roentgenographic examination of the spine disclosed normal vertebrae. In view of the semihysterical condition of the patient, a gastric analysis was not attempted.

On September 28, 1942 a biopsy was removed from the central portion of the umbilicus under local anesthesia. Histological examination of this biopsy showed adenocarcinoma, grade IV, involving the skin of the umbilicus. It was the impression of the pathologist (L. P.) that the tumor was probably of gastrointestinal origin, because of the presence of occasional signet-ring type cells distended with mucus which were seen among the tumor cells. On October 2, 1942 an exploratory laparotomy (by L. E. L.) was performed. The omentum was adherent to the umbilicus and an area of nodular masses could be felt in the parietal peritoneum. The omentum was studded with metastatic nodules of carcinoma, particularly near its gastric attachment. The stomach revealed an extensive scirrhous cancer involving the pyloric half which completely encircled the distal third. A number of hard tumor nodules were felt in the parietal peritoneum near the umbilicus and in the gastrohepatic ligament. The gall-bladder and duodenum were normal.

The postoperative condition of the patient was poor, she became gradually weaker and died November 11, 1942, apparently from bronchopneumonia. Permission for an autopsy was refused.

Summary

1. A case of metastatic involvement of the umbilicus from inoperable carcinoma of the stomach, apparently the thirty-eighth reported in the medical literature, is presented.

2. It is believed that such cases are not so rare as the literature indicates and more careful examination of the umbilicus for metastasis in suspected cancer of the stomach is recommended.

We are indebted to Miss Florence L. Wickes, Reference Librarian, Lane Medical Library, Stanford University School of Medicine, San Francisco, for her assistance.

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CORRECTION

Dosage of Acetyl-beta-methyl-choline Chloride

In the article by Captain Julius R. Pearson and Lt. Colonel Albert W. Wallace, "The Syndrome of Paroxysmal Tachycardia with Short P–R Interval and Prolonged QRS Complex, with Report of Two Cases," in the Annals of Internal Medicine, 1944, Volume 21 (November), page 838, it is stated "he was given 0.2 gm. acetyl-beta-methyl-choline chloride subcutaneously." This figure (which was a typographical error in the manuscript) should read 0.02 gm. The larger quantity would be a dangerous overdose. We are indebted to the Medical Department of Merck and Co., Inc., for calling attention to this oversight.

EDITORIAL

THE SITE OF ANTIBODY FORMATION

THE problems concerned with the formation of antibodies have stimulated the interest of investigators for many years. One of the most interesting of these concerns the site of antibody formation and the types of cells concerned in the process. Is this a general property of all or most of the cells of the body, or is it restricted to certain special types of cells? In spite of a great deal of speculation and study, relatively little direct evidence in answer to these questions has been obtained.

Since the observations of Metschnikoff and his followers over 50 years ago, attention has been centered largely on the cells of the reticuloendothelial system. The fact that the macrophages as well as the polymorphonuclear neutrophilic leukocytes engulf and digest bacteria and other foreign cells as well as absorb certain foreign substances in colloidal suspension naturally suggested that these cells are also concerned in the elaboration of the specific antibodies which subsequently appear in the circulation. Although phagocytosis and digestion of foreign cells by the reticuloendothelial cells is easily demonstrable, there is little or no direct evidence of antibody production by them. Considerable indirect evidence for this has been advanced, however.

Some observers have reported that following an injection of antigen, antibodies appeared in higher concentration in the spleen and bone marrow than in the blood. Removal of the spleen (in guinea pigs, and dogs) a few days after injection of an antigen reduced significantly the antibody titer subsequently attained by the animal, as compared with nonsplenectomized control animals. Topley [1] showed that if the spleen from a rabbit so treated is ground up and injected into a normal rabbit, the latter will develop antibodies (in low titer) which appear and disappear more rapidly than in an animal primarily inoculated with the antigen. Furthermore, such an animal will not show an accelerated response to a subsequent injection of the same antigen. This suggested to Topley that the reticuloendothelial cells in the splenic tissue injected did not liberate antigen which could act on the cells of the new host, but that the antibodies which appeared in the latter were produced in and liberated by the reticuloendothelial cells in the splenic pulp which had been injected.

One of the principal arguments which has been advanced in support of the view that the reticuloendothelial cells are the site of antibody formation is the effect produced by "blockade" of the reticuloendothelial system. If an animal is injected intravenously with india ink or some suitable material in colloidal suspension, the reticuloendothelial cells generally become

[1] TOPLEY, W. W. C.: Rôle of spleen in production of antibodies, Jr. Path. and Bact., 1930, xxxiii, 339–351.

engorged with this material. If an antigen is then injected, there may be a partial or complete lack of antibody formation which is commonly attributed to the preoccupation of the reticuloendothelial cells with the colloidal particles previously administered.

Sabin [2] made some interesting observations on the behavior of macrophages which had ingested visible aggregates of a dye-protein, which have been advanced in support of the view that the macrophages produce antibodies. In supravital preparations she observed the gradual removal of the dye from these particles, and the disappearance of the protein particles which presumably had gone into solution in the cytoplasm. Also after these particles had disappeared and at a time when antibodies were appearing in the blood, she observed shedding of fragments of the cytoplasm by the macrophages without apparent injury to the latter, which she interpreted as an excretion or expulsion of antibody by the cell. There is, however, no direct evidence that these fragments contained antibody. Furthermore, as this phenomenon was not observed in perfectly fresh preparations, the possibility seems not excluded that this represents an early manifestation of cell degeneration rather than a physiological mechanism. A similar shedding of cytoplasm by lymphocytes has been described (Downey and Weidenreich).

Attempts have been made to demonstrate antibdy formation in tissue cultures. The most convincing results have been obtained by cultivation of tissues taken from animals which had been previously injected with antigen. Thus (among others) Meyer and Loewenthal [3] demonstrated the formation of agglutinins for typhoid bacilli in cultures of the spleen, lymph nodes and milk spots of the omentum of rabbits which had been injected with typhoid bacilli. The experiments previously discussed were not so designed as to determine which cells in the tissues examined produced the antibody demonstrated. Since the milk spots, however, are stated to contain only reticuloendothelial cells and a few fibroblasts, this appears to be the most direct evidence available of the formation of antibodies by reticuloendothelial cells.

Relatively little attention has been devoted in the past to the part lymphocytes may play in the defense mechanism. Unlike the reticuloendothelial cells and the neutrophilic leukocytes, they are not phagocytes. For many years, however, Bunting [4] in particular has maintained that the lymphocytes play an important rôle in the defense against toxins and soluble antigens. The evidence for this, also, has been largely indirect. When toxins gain access to the body tissues, they are largely taken up into the lymph and pass into and through the regional lymph nodes where they appear to be ab-

[2] Sabin, F. R.: Cellular reactions to a dye-protein with a concept of the mechanism of antibody formation, Jr. Exper. Med., 1939, lxx, 67–82.

[3] Meyer, K., and Loewenthal, H.: Untersuchungen über Antikörperbildung in Gewebekulturen, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1928, liv, 409–419.

[4] Bunting, C. H.: Cell reactions in resistance and immunity, Wisconsin Med. Jr., 1925, xxiv, 305–308.

sorbed or filtered out to a greater or lesser extent. In high concentrations they may cause necrosis of the cells in the nodes, but in lesser concentration, under conditions more favorable to the host, they stimulate a proliferation of the lymphocytes which is coincident with the development of antibodies. In acute infections, during the early stage there is usually an increase in granulocytes and an actual reduction in lymphocytes. In cases with a favorable outcome, however, there is often a well marked lymphocytosis as recovery sets in, approximately coincident with the appearance of antibodies in the circulation. In chronic infections like tuberculosis, a lymphocytosis is common in patients whose disease is running a favorable course, whereas an increase in monocytes at the expense of the lymphocytes suggests an active progressive infection.

Bunting also believes that the distribution of lymphocytes in inflammatory lesions indicates their importance in the defense mechanism. "The position of the normal lymphoid accumulations, the grouping of lymphocytes which are nonphagocytic cells, about the tubercle, the gumma and acute inflammatory foci, forming a protective ring through which toxins must filter before reaching vital tissues; the curve of reaction in diseases followed by immunity; all these point toward a chemical function for the cell." [4]

Procedures such as exposure to roentgen-ray which destroy lymphoid tissue, diminish resistance and lower antibody production in animals. On the contrary, if lymphoid tissue is stimulated by exposure of animals to dry heat, antibody production is greater than normal.

More direct evidence of the formation of antibodies in lymph nodes was furnished by McMaster and Hudack.[5] They injected bacterial 'vaccine' intradermally into the ears of mice, and several days later demonstrated antibodies in the regional lymph nodes in higher concentration than in the blood. That this was not due to a concentration in the lymph nodes of circulating antibody which had been formed elsewhere was proved by injecting different types of vaccine into the two ears of the same mouse. Then the regional lymph node contained antibodies for the organism injected into the homolateral ear, and none or much smaller quantities of antibody for the species injected into the opposite ear.

Ehrich and Harris[6] made similar studies in rabbits, injecting typhoid vaccine into the foot pad on one side, and sheep erythrocytes on the other. They were able to examine the afferent and efferent lymph as well as the regional node itself. They observed well marked hyperplasia of the lymphocytes in the node and a marked rise in the cell count of the efferent as compared with the afferent lymph (about 5,000 to 67,000), over 99 per cent of which were lymphocytes. After two to four days, antibodies ap-

[5] McMaster, P. D., and Hudack, S. S.: The formation of agglutinins within lymph nodes, Jr. Exper. Med., 1935, lxi, 783–805.

[6] Ehrich, W. E., and Harris, T. N.: The formation of antibodies in the popliteal lymph nodes in rabbits, Jr. Exper. Med., 1942, lxxvi, 335–357.

peared in the efferent lymph, in much higher concentration than in the afferent lymph and at first higher than in the blood, whereas they found none or only small amounts of antibody for the antigen injected into the contralateral foot.

In a more recent study, Harris et al.,[7] have secured more direct evidence as to the part played by the lymphocytes in this reaction. From rabbits injected as in the preceding study they obtained efferent lymph and removed the lymphocytes from the lymph by centrifugalization. They then compared the antibody titer in the lymph and in extracts of the leukocyte sediment. The titer of the latter was consistently greater than that of the lymph, in most cases from two to eight times higher. By appropriate control tests it was shown that the lymphocytes tend to give up antibodies to the lymph in which they are suspended. On the other hand, they could detect no absorption or adsorption by the lymphocytes of antibodies present in the lymph, either in vivo or in vitro.

This evidence of the formation of antibodies by lymphocytes seems convincing. Obviously it does not exclude the possibility of their production by macrophages as well. Ehrich,[8] however, has pointed out that the latter possibility is based on inferences only, and not on direct proof. He suggests that the facts which are known regarding the activities of the macrophages are equally in harmony with the theory that the latter serve to engulf and digest the foreign antigen and so alter it that it can be utilized by the lymphocytes in the actual process of antibody production.

This new work is interesting in directly demonstrating the importance of the lymphocyte in protecting the body from infection. Without doubt the macrophage, the granular leukocyte and the lymphocyte should be regarded as a team, of substantially equal importance, whose coördinated activities are essential for effective defense against infection.

[7] Harris, T. N., Grimm, E., Mertens, E., and Ehrich, W. E.: The rôle of the lymphocyte in antibody formation, Jr. Exper. Med., 1945, lxxxi, 73–83.

[8] Ehrich, W. E., and Harris, T. N.: The site of antibody formation, Science, 1945, ci, 28–31.

REVIEWS

Roentgen Treatment of Diseases of the Nervous System. By CORNELIUS G. DYKE, M.D., F.A.C.R., and LEO M. DAVIDOFF, M.D., F.A.C.S. 198 pages; 24 × 15.5 cm. 1942. Lea and Febiger, Philadelphia. Price, $3.25.

In a small volume, the authors present a concise review and summary of radiation therapy of neoplasms attacking the central nervous system. The various types of new growths are considered, and in a few brief statements, all the significant literature pertaining to each kind of tumor is summarized. Following this, Drs. Dyke and Davidoff present their experiences in radiation therapy to the different lesions. They not only include the results of other workers and themselves, but state the important details of treatment, such as voltage, target-skin distance, milliamperage and filtration uses by each therapist.

Numerous case histories are recorded, which leave no doubt but that favorable results are to be expected following radiation therapy in medulloblastomas, gliomas of the optic chiasm, xanthomatosis, and a few primary spinal extradural sarcomas. Of still more interest than the preceding information are the findings of the authors that certain kinds of tumors long believed to be radio-resistant will often respond to deep roentgen-rays. Hope can now be extended to those patients who are harboring craniopharyngiomas, chromophil adenomas, and neurofibroma of the spine.

Prophylactic radiation of the spinal cord is advocated as a routine regime when medulloblastomas and ependymomas are diagnosed, even in the absence of clinical spinal involvement. In the doses suggested, no harm is likely to ensue from the treatments and silent metastases may be eradicated.

Considering the importance of the field covered and the clear method of presenting the material, anyone who reads this small volume will be adequately compensated for the effort.

D. J. B.

Atlas of the Blood in Children. By KENNETH D. BLACKFAN, M.D., and LOUIS K. DIAMOND, M.D. 320 pages; 28 × 20.5 cm. 1944. Commonwealth Fund, New York. Price, $12.00.

The text consists of brief but complete descriptions of the various disease entities. The more important hematological disorders encountered in children are all included, with illustrative case reports and a selected bibliography. For simplicity it is divided into: (1) The Blood Cells. (2) The Erythrocytes in Anemia. (3) The Leukocytes in Disease. (4) Leukemia. (5) Platelets.

The 70 plates are beautifully done by the pediatrician and artist, Dr. Leister. With each plate there is an accompanying key illustration which accurately describes it.

The Atlas is written and arranged with such simplicity that reading is very enjoyable and readily assimilated. It is a real tribute to Dr. Blackfan and to the many fine publications that he and Dr. Diamond have jointly made.

W. M. S.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Atlas of the Blood in Children. By KENNETH D. BLACKFAN, M.D., and LOUIS K. DIAMOND, M.D. 320 pages; 28 × 20.5 cm. 1944. Commonwealth Fund, New York. Price, $12.00.

The Embryology of Behavior. By ARNOLD GESELL, M.D. 289 pages; 23.5 × 16 cm. 1945. Harper & Brothers, New York. Price, $5.00.

The Pathology of Internal Diseases. 4th Edition. By WILLIAM BOYD, M.D., LL.D., M.R.C.P., Ed., F.R.C.P., Lond., Dipl., Psych., F.R.S.C. 857 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia. Price, $10.00.

Endocrinology of Women. By E. C. HAMBLEN, B.S., M.D., F.A.C.S. 571 pages; 26 × 17 cm. 1944. Charles C. Thomas, Springfield, Illinois. Price, $8.00.

Textbook of Medical Treatment. 3rd Edition. By VARIOUS AUTHORS. Edited by D. M. DUNLOP, B.A. (Oxon.), M.D., F.R.C.P. (Edin.), M.R.C.P. (Lond.), L. S. P. DAVIDSON, B.A. (Camb.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.), and J. W. MCNEE, D.S.O., D.Sc., M.D. (Glas.), F.R.C.P. (Edin.), F.R.C.P. (Lond.). With a foreword by the late PROFESSOR A. J. CLARK, B.A. (Camb.), M.D., D.P.H., F.R.C.P. (Lond.), F.R.S. 1218 pages; 22 × 14.5 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $8.00.

American Medical Practice in the Perspectives of a Century. By BERNHARD J. STERN, Ph.D. 156 pages; 21.5 × 14 cm. 1945. Commonwealth Fund, New York. Price, $1.50.

Medical Uses of Soap. Edited by MORRIS FISHBEIN, M.D. 182 pages; 23.5 ×15.5 cm. 1945. J. B. Lippincott Company, Philadelphia. Price, $3.00.

Medical Diseases of War. By SIR ARTHUR HURST, M.A., D.M., F.A.C.P. With the coöperation of H. W. Barber, M.A., M.B., F.R.C.P., H. B. F. DIXON, M.C., M.D., D.T.M. and H., F.R.C.P., E. H. R. HARRIES, M.D., F.R.C.P., D.P.H., F. A. KNOTT, M.D., F.R.C.P., MELVILLE D. MACKENZIE, M.D., D.T.M. and H., T. A. Ross, M.D., F.R.C.P., and ARNOLD W. STOTT, M.A., F.R.C.P. 511 pages; 22 × 14.5 cm. 1944. Williams and Wilkins Company, Baltimore. Price, $6.00.

Etiology, Diagnosis and Treatment of Amebiasis. By CHARLES F. CRAIG, M.D., Colonel U. S. Army, retired. 332 pages; 24 × 16 cm. 1944. Williams & Wilkins Company, Baltimore. Price, $4.50.

The Story of a Hospital. The Neurological Institute of New York, 1909–1938. By CHARLES A. ELSBERG, M.D. 174 pages; 19.5 × 13 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $3.50.

Lead Poisoning. By ABRAHAM CANTAROW, M.D. and MAX TRUMPER, Ph.D. 264 pages; 23.5 × 16 cm. 1944. Williams & Wilkins Company, Baltimore. Price, $3.00.

The British Journal of Surgery. Special Issue: Penicillin in Warfare. Chairman of Editorial Committee: GEORGE E. GASK (London). 224 pages; 25.5 × 18.5 cm. 1944 (Supplement to Vol. xxxii, no. 125, of the British Journal of Surgery, July 1944). Williams and Wilkins Company, Baltimore. Price, $2.50, paper cover, supply limited.

The Reticulo-Endothelial System in Sulfonamide Activity. By FRANK THOMAS MAHER, Ph.D. 232 pages; 27.5 × 20.5 cm. 1944. University of Illinois Press, Urbana, Illinois. Price, $2.50 paper bound; $3.00 cloth bound.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1945–46

In accordance with the By-Laws of the American College of Physicians Article I, Section 3, the following nominations for the elective offices, 1945–46, are herewith announced and published:

President-Elect ..... Brigadier General Hugh J. Morgan, Washington, D. C.
First Vice-President ..... Dr. James J. Waring, Denver, Colorado
Second Vice-President .... Dr. A. B. Brower, Dayton, Ohio
Third Vice-President ..... Dr. T. Homer Coffen, Portland, Oregon

The election of nominees shall be by the Fellows of the College at its Annual Business Meeting, St. Louis, Mo., May 5, 1945. The above nominations do not preclude nominations made from the floor at the Annual Business Meeting itself. Nominations for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting.

Respectfully submitted,

Francis G. Blake, New Haven, Conn.
Robert O. Brown, Santa Fe, N. M.
John H. Musser, New Orleans, La.
John W. Scott, Edmonton, Alberta
Walter W. Palmer, *Chairman*, New York, N. Y.
Committee on Nominations

Additional Members on Active Military Duty

The following additions of members of the American College of Physicians on active military duty in the Medical Corps of the Army, Navy and Public Health Service are herewith recorded. Previously reported were the names of 1,721 members, which brings the gross number now to 1,845.

Ashe, William Francis, Jr.
Atwater, John Spencer
Autry, Daniel Hill
Baldwin, Robert Sherman
Barnum, Glenn Lewis
Bean, William Bennett
Bell, James Roeder
Bortz, Donald Worcester
Boyer, Norman Howard
Brewen, Stewart Ferdinand
Brownley, Harvey Christian
Brownstein, Samuel R.
Brumm, Harold J.
Cain, James Clarence
Callaway, James Willis
Chapman, William Holmes, Jr.
Cheskin, Louis Joseph
Cogan, Michael Aaron
Conway, William Hynes
Cook, Joseph Russell
Coombs, Frederick Stanley, Jr.
Darnall, Charles Milton
Davie, John Holmes
Davis, Hal
Drake, Ellet Haller
Dunham, Charles Little
Durkin, John Keenan
Everett, Peter, III
Finkelstein, David
Flynn, Joseph Eugene
Friedland, Elmer
Friedman, Maurice Harold
Friend, Dale G. F.
Frisch, Robert Abraham
Frist, Thomas Fearn
Geddis, James Thomas J.

Glenn, Paul Mitchell
Glidden, Henry Spencer
Goldstein, Milton Joseph
Goldstein, Philip
Grier, George Smith, III
Grishaw, William Harry
Haft, Henry H.
Herndon, James Henry
Hinnant, Iredell Melvin
Hoffman, Byron Jay
Hollands, Robert Arthur
Humphrey, Arthur Allen
Hurevitz, Hyman M.
Israel, Harold Louis
Kammerer, William Henry
Kaplan, Bernard Irving
Kaplan, George
Kirsner, Joseph Barnett
Kirstein, Melvin B.
Klainer, Max Joseph
Kopp, Israel
Kossmann, Charles Edward
Krainin, Philip
Learner, Norman
Levy, Joseph
Lieder, Louis Eugene
Lief, Victor Filler
Lindahl, Wallace William
Lipton, Harry Robert
Litwins, Joseph
Lozner, Eugene Leonard
Lutz, Edgar Harvey
Macdonald, Hugh
MacNiel, Alec Cameron
McDaniel, Lewis Tillman
McLaughlin, James Alphonsus
McLochlin, Ralph Edwin
Medoff, Joseph
Miller, John Fleek
Mills, Charles Selby
Moloney, William Curry
Monaco, Thomas Clifford
Myerson, Samuel
Myhre, William Norwood
Norman, James Kindred
Olsen, Alonzo Young
Page, Sidney Grey, Jr.
Paull, Ross
Penner, Sidney Lincoln
Pignataro, Frank P.
Popper, Hans
Porter, Reno Russell
Post, Joseph
Priddle, William Welmore
Randall, William Spears, Jr.
Raynolds, Arthur Hidden
Read, William Alexander
Robertson, Alexander David
Rosenberg, David Harry
Rueger, Milton Jerome
Sauer, William George
Scheifley, Charles Holland
Shuler, James Benjamin
Sittler, William Walter
Smith, Richard Henry
Spivey, Russell Jordan
Souders, Carlton R.
Storey, William Edward
Sullivan, William John
Suter, James Marion
Sweetser, Horatio B., Jr.
Sweigert, Charles Francis
Tice, James W.
Townsend, Stuart Ross
Vance, William Clifford
Van Ormer, William Alfred
Walker, Douglass Willey
Wallace, Joseph James
Waller, William Kennedy
Waud, Sydney Peyster
Wendkos, Martin Howard
Wever, George Kuhn
White, Benjamin V.
Whitehead, Duncan
Wolfram, Julius
Wood, William Hoge, Jr.
Worsley, Thomas Luther, Jr.
Zavod, William Abraham

New Life Members

The following Fellows of the College have recently subscribed to Life Membership and are listed in the order of receipt of subscriptions:

A. F. R. Andresen, Brooklyn, N. Y.
Henry A. Christian, Brookline, Mass.
Erwin D. Funk, Wyomissing, Pa.

George M. Levitas, Westwood, N. J.
Eugene E. Marcovici, New York, N. Y.
Samuel T. Nicholson, Jr., Pottstown, Pa.
Ralph L. Shanno, Forty Fort, Pa.
Carl Edward Johnson, Morgantown, W. Va.
Frank B. Kelly, Chicago, Ill.
David L. Perry, New Castle, Pa.

GIFTS RECEIVED BY THE COLLEGE LIBRARY

Reprints

J. Heinz Ahronheim, F.A.C.P., Captain, (MC), AUS—1 reprint.
J. Edward Berk, F.A.C.P., Captain, (MC), AUS—2 reprints.
Dr. J. Bailey Carter, F.A.C.P., Chicago, Ill.—2 reprints.
Earl R. Denny, F.A.C.P., Lieutenant Colonel, (MC), AUS—2 reprints.
Dr. Richard DeM. Kepner, F.A.C.P., Honolulu, T. H.—2 reprints.
Robert H. Mitchell, (Associate), Lieutenant Colonel, (MC), AUS—1 reprint.
Michael Peters, (Associate), Captain, (MC), AUS—1 reprint.
Maurice A. Schnitker, F.A.C.P., Major, (MC), AUS—1 reprint.
Dr. George X. Schwemlein, (Associate), U.S.P.H.S., Chicago, Ill.—1 reprint.
James S. Sweeney, F.A.C.P., Colonel, (MC), AUS—1 reprint.
Dr. Charles R. Thomas, F.A.C.P., Chattanooga, Tenn.—1 reprint.
Dr. I. Milton Wise, F.A.C.P., Mobile, Ala.—2 reprints.

Dr. W. P. Anderton, F.A.C.P., has succeeded the late Dr. Peter Irving, F.A.C.P., as Secretary of the Medical Society of the State of New York. Dr. Irving died on December 28, 1944.

The annual meeting of the Wisconsin Heart Association was held at the Wisconsin General Hospital, Madison, December 16, 1944. Among those contributing were: Dr. O. O. Meyer, F.A.C.P., Madison, clinic on "Subacute Bacterial Endocarditis Treated with Penicillin and Dicoumarol"; Dr. C. M. Kurtz, F.A.C.P., Madison, clinic on "Interesting Cardiac Cases"; Dr. C. F. Midelfort, (Associate), Eau Claire, Wis., "Studies on the Carotid Sinus"; Lt. Col. C. S. Highley, (MC), AUS, F.A.C.P., "Intravenous Salicylate in the Treatment of Rheumatic Fever"; Major F. S. Coombs, (MC), AUS, (Associate), "Toxicity of Sodium Salicylate"; Major H. A. Warren, (MC), AUS, (Associate), "Sulfadiazine in the Prophylaxis of Rheumatic Fever"; Dr. N. C. Gilbert, F.A.C.P., Chicago, "Coronary Disease"; Dr. Vincent Koch, F.A.C.P., Janesville, Wis., "Salt-free Diet and High Fluid Intake in the Treatment of Cardiac Decompensation."

Dr. George X. Schwemlein, (Associate), and Dr. R. M. Craig, (Associate), were recently appointed co-medical directors of the Chicago Intensive Treatment Center.

Mr. Edward R. Loveland, Executive Secretary, American College of Physicians, was recently elected to Honorary Membership in the Omaha Mid-West Clinical Society.

The Hospital for Joint Diseases, 1919 Madison Ave., New York City, announced recently its desire to obtain House Staff appointments to fill twelve places on the General Rotating Service. Eight interns are desired to begin July 1, August 1, September 1, and October 1, 1945, each for a nine months' period. One-half of the number appointed may be permitted to continue for another nine months as Junior Residents, and thereafter, one-half of the number of Junior Residents may be continued for another nine months as Senior Residents, in accordance with the Allocation Plan of the Procurement and Assignment Service.

Major Sidney Schnur, (MC), AUS, (Associate), who preceding the war was a physician in Houston, Tex., has been cited for meritorious conduct with the 7th Bombardment Group and India Task Force from May, 1942, through August 27, 1943. The citation was signed by General Joseph Stilwell, and the Bronze Star, eighth ranking War Department medal, was awarded Major Schnur. The citation read: "Major Schnur showed great initiative, ingenuity and ability in maintaining the health of the command. By successfully raising the sanitation level of the Air Force field installations to an unusual degree, by initiating and following through a malaria control program which has actually controlled the disease, by persistent efforts and novel procedures in the control of venereal diseases, by improving the quality of food served in field messes through introduction of new methods of procurement and distribution, by devising and supplying escape first aid kits to combat personnel, and by his continuous research in various fields of aviation medicine, Major Schnur lowered the noneffective rate from disease to a bare minimum. Major Schnur's devotion to duty and his successful and tireless efforts in the fields of health, hygiene and sanitation reflect great credit on the Armed Forces of the United States."

Colonel William S. Middleton, (MC), AUS, F.A.C.P., Consultant in Medicine in the European Area, was one of the eight alumni of the University of Pennsylvania to receive special recognition for "outstanding service to the University during the recent past" at Founder's Day meeting of the University on January 20, 1945.

Major General George F. Lull, (MC), USA, F.A.C.P., Deputy Surgeon General, delivered the commencement address of the Southwestern University Medical School, Dallas, Tex., recently.

Pointing out that treatment and evacuation of wounded must go hand in hand, General Lull described how the problem of saving lives varies in different theaters of war. He contrasted the carefully planned, smoothly regulated chain of evacuation from the Normandy Beachhead with the difficulties under which wounded were evacuated in some Southwest Pacific areas where "small portable hospitals had to be carried forward over mountain trails through jungle to the rear of the fighting troops" and "cases were operated on in the jungle and had to be carried for miles until they could be placed in jeeps."

The reasons for lower mortality rates compared to World War I may be charged to three things, General Lull said: better surgery, done earlier; blood plasma; and chemotherapy. In connection with the latter he stated that the results of the so-called sulfa drugs have been much more spectacular in medicine than in surgery, and cited the lowering of the mortality rate for cerebrospinal meningitis of meningococcic origin to less than one-fourth what it was in World War I, and that of pneumonia

from 35 per cent in the last war to under 1 per cent. Penicillin, too, he said, had proved its worth in many types of medical cases, notably in the venereal diseases. "Of course," he added, "one of the most important functions of the Medical Department is the prevention of disease. Great strides have been made in this field during the present war."

The following promotions in the Medical Corps of the Army have been announced:

Lieutenant Colonel to Colonel

Oscar Blitz, (Associate), New Orleans, La.
Hugh Richmond Gilmore, Jr., F.A.C.P., Emlenton, Pa.

Major to Lieutenant Colonel

Clarence L. Gardner, Jr., F.A.C.P., Aurora, Ill.
Charles E. Lemmon, F.A.C.P., Detroit, Mich.
Joseph O. Weilbaecher, Jr., F.A.C.P., New Orleans, La.
James S. McQuiston, F.A.C.P., Cedar Rapids, Iowa.
David Robert Sacks, F.A.C.P., San Antonio, Tex.
John Mitchell Willis, Jr., F.A.C.P., Philadelphia, Pa.

The Dallas Southern Clinical Society will hold its fifteenth annual conference at Hotel Adolphus, Dallas, March 19–22, 1945. Among guest speakers will be Dr. George W. Thorn, F.A.C.P., Boston, Medicine; Dr. Charles A. Doan, F.A.C.P., Columbus, Medicine; Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., Gastro-Enterology; Dr. William H. Sebrell, Jr., F.A.C.P., Washington, D. C., Basic Science.

Dr. Robert H. Felix, F.A.C.P., Washington, D. C., is President-Elect of the Medical Correctional Association. He has also been appointed Medical Director in charge of the Mental Hygiene Division, Bureau of Medical Service, U. S. Public Health Service, succeeding Dr. Lawrence Kolb, F.A.C.P., retired.

Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Professor of Medicine at the University of Georgia School of Medicine, has been commissioned with the United Nations Relief and Rehabilitation Administration as Chief Counsel in Nutrition for Western Europe. He holds the rank of Colonel, and will have charge of organizing the health service of all nations west of the Balkans.

Dr. Carroll Lockard, F.A.C.P., Baltimore, is President of the Medical and Chirurgical Faculty of Maryland, the state medical society.

Under the presidency of Dr. Victor Schulze, F.A.C.P., San Angelo, and the secretaryship of Dr. Walter B. Whiting, F.A.C.P., Wichita Falls, the Texas State Heart Association will meet at Galveston May 7.

Dr. William S. McEllroy, F.A.C.P., Dean of the University of Pittsburgh School of Medicine, has been appointed medical survey advisor, succeeding General Charles

R. Reynolds, F.A.C.P., of Harrisburg, who resigned to become a member of the staff of the American College of Surgeons. Dr. McEllroy will be called upon to advise the Pennsylvania Selective Service Headquarters on various phases of the Medical Survey Program.

Dr. Walter L. Bierring, F.A.C.P., Des Moines, State Health Commissioner for Iowa, spoke at the dedication of the Raymond Blank Hospital for Children in Des Moines on December 3. This hospital is the first constructed in Iowa exclusively for the treatment of children.

Dr. Clarence E. Hufford, F.A.C.P., Cleveland, was recently made President of the Ohio State Radiological Society.

Dr. Charles A. Doan Appointed Dean, Ohio State University

Dr. Charles A. Doan, F.A.C.P., who has served since 1936 as Chairman of the Department of Medicine at Ohio State University College of Medicine, Columbus, has been appointed Dean. Dr. Doan graduated in medicine from Johns Hopkins University School of Medicine in 1923. He went to Ohio State University in 1930 as Professor of Medicine and Director of the Department of Medical and Surgical Research.

Dr. Warfield T. Longcope, F.A.C.P., Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, delivered the first John Auer Lecture at the St. Louis University School of Medicine, November 29, his title being "Allergic and Toxic Reactions of the Sulfonamide Drugs."

Dr. William W. Herrick, F.A.C.P., Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, and Attending Physician to the Presbyterian Hospital, has been elected President of the New York Academy of Medicine for a term of two years. Dr. Herrick has had a distinguished career. He was one of the early Fellows of the American College of Physicians and at one time served on its Board of Regents.

Dr. Edward Kupka, F.A.C.P., has accepted an appointment as Medical Director of the La Vina Sanatorium, La Vina, Calif., and of the Hastings Foundation for Tuberculosis Research, Pasadena, to succeed Dr. Carl R. Howson, F.A.C.P., resigned.

Dr. James Howard Means, F.A.C.P., Jackson Professor of Clinical Medicine at Harvard Medical School, Boston, recently addressed the Baltimore City Medical Society on "Hyperophthalmopathic Graves' Disease."

Dr. George W. McCoy, F.A.C.P., New Orleans, and Colonel Thomas T. Mackie, (MC), AUS, F.A.C.P., New York, have been elected Vice President and Treasurer, respectively, of the American Academy of Tropical Medicine.

Dr. Philip Levine, F.A.C.P., Linden, N. J., delivered the first Reginald Knight Smith Lecture at Mount Zion Hospital, San Francisco, January 11, on "Rh Factor and Its Clinical Significance." The lectureship has been inaugurated in memory of the late Dr. Smith, who was Chief of the Division of Obstetrics at the Mount Zion Hospital from 1909 to 1937.

Commander F. J. Braceland, (MC), USNR, F.A.C.P., Psychiatry Branch of the Professional Division of the Bureau of Medicine and Surgery, has been appointed an examiner on the American Board of Psychiatry.

Colonel John Minor, (MC), AUS, F.A.C.P., formerly Chief of the Medical Service at the Woodrow Wilson General Hospital, Staunton, Va., is now Consultant in Medicine to the Third Service Command, Baltimore.

Dr. Ward Darley, F.A.C.P., is Director of the Rheumatic Fever Diagnostic Service established recently by the Denver Area War Chest. The objective is to locate cases of rheumatic fever and rheumatic heart disease among children and to have them referred to proper sources for care. The Diagnostic Service does not offer treatment. All results of examinations are mailed to the physician to whom the case is referred. No charge is made for the service.

Dr. Daniel J. Glomset, F.A.C.P., Des Moines, Dr. George H. Coleman, F.A.C.P., Chicago, and Dr. Grant H. Laing, F.A.C.P., Chicago, are Vice President, Secretary and Treasurer, respectively, of the Chicago Institute of Medicine.

Dr. Alvis Greer, F.A.C.P., Houston, has been appointed Editor-in-Chief of the *Medical Record and Annals.*

Colonel G. G. Duncan, (MC), AUS, F.A.C.P., formerly Chief of Medical Service at the England General Hospital, Atlantic City, N. J., is now assigned as Consultant in Medicine, Headquarters, Second Service Command, Governor's Island, N. Y.

Lt. Col. F. R. Dieuaide, F.A.C.P., Chief of the Tropical Disease Treatment Branch, Office of the Surgeon General, who recently returned from a three months' visit in three Pacific Theaters, reported a small epidemic of skin diphtheria, in the New Hebrides, which was brought under early control.

It is thought the epidemic arose from carriers, the bacilli usually being carried in arm or leg wounds from which the organisms could be transferred readily to skin lesions in other persons or to the throats of susceptible soldiers.

Individuals afflicted with this rare disease usually do not show serious effects, said Colonel Dieuaide, although neuritis sometimes develops and there are occasional heart disturbances. The symptoms generally disappear if the patient is put at rest, the lesions properly cleaned, and a sterile, wet dressing applied. Penicillin has been used but it is not necessary, he said, unless other bacteria are present. A small

dose of antitoxin is enough to protect most patients from any serious consequence to themselves.

The great importance of skin diphtheria, Colonel Dieuaide explained, lies in the danger that it may cause epidemics of ordinary diphtheria in soldiers, 45 to 50 per cent of whom are susceptible. The Medical Department has therefore taken prompt and effective steps to control the spread of the milder disease.

Major John R. S. Mays, (MC), AUS, (Associate), Baltimore, Md., has been appointed Consultant in Neuropsychiatry for the Burma Theater of Operations. Prior to his overseas assignment, Major Mays was Chief of the Neuropsychiatric Section at McGuire General Hospital, Richmond.

Dr. Bernard E. McGovern, F.A.C.P., presented a paper before the San Fernando Valley Branch of the Los Angeles County Medical Association, Burbank, Calif., entitled, "The Diagnosis and Differential Diagnosis of Pulmonary Tuberculosis."

Medical Department Trains Medical Administrative Corps Officers as Battalion Surgeon Assistants

In order to relieve the critical shortage of doctors, the Medical Department has recently increased its quota for admission to officer candidate schools and has initiated a new program of training graduate administrative officers as battalion surgeon assistants. Between now and April 1945 appointments will be made in the Medical Administrative Corps after seventeen weeks training at Camp Barkeley, Texas and Carlisle Barracks, Pennsylvania.

From among these graduates, officers with appropriate backgrounds will be selected to receive six weeks additional training at Camp Barkeley for duty assisting battalion surgeons. The special training consists principally of advanced first aid which will qualify these officers to relieve battalion surgeons of details and thus permit the surgeons time for purely medical and surgical work.

General Morgan Visits Hospitals

Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant in Medicine, Office of The Surgeon General, recently returned from visiting Woodrow Wilson General Hospital, Staunton, Va., McGuire General Hospital, Richmond, Va., and Lawson General Hospital, Atlanta, Ga. He also attended the annual meeting of the Kentucky State Medical Association on September 19 in Lexington, Ky., where he participated in a symposium on new methods of administering penicillin.

Incidence of Poliomyelitis Among U. S. Troops

In the two-week period ending September 2, 1944, 20 cases of poliomyelitis were reported by Army installations in the United States. This represents a slightly higher incidence than for the corresponding period last year. The total incidence since the first of the year is somewhat lower than in the corresponding 8-month period of 1943. Although most of the cases have occurred in the states which have a high civilian incidence of the disease they have been widely scattered.

Dr. Caleb O. Terrell, F.A.C.P., Fort Worth, has been made a member of the Board of Regents of the University of Texas.

A.C.P. Postgraduate Courses, Spring, 1945

Below appears the full and detailed outline of Course No. 1, Cardiology, and Course No. 2, Mechanics of Disease. The detailed outlines of other courses have not yet been completed by the Directors, and, therefore, are not ready for publication at this date (January 17, 1945).

Refer to a full page announcement of the Schedule of Courses in the advertising section in the back of this issue.

The Program of Postgraduate Courses of the American College of Physicians Has Been Approved by the Office of Defense Transportation.

Course No. 1—Cardiology

(March 19–24, 1945)

College of Physicians and Surgeons, Columbia University

630 West 168th Street

New York, New York

Robert L. Levy, M.D., F.A.C.P., *Director*

(Maximal Registration, 50)

Officers of Instruction

Dana W. Atchley, M.D., Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Associate Visiting Physician, Presbyterian Hospital.

George Baehr, M.D., F.A.C.P., Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Director of Clinical Research, Mt. Sinai Hospital.

Alvan L. Barach, M.D., F.A.C.P., Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Assistant Attending Physician, Presbyterian Hospital.

Lois C. Collins, M.D., Associate in Radiology, College of Physicians and Surgeons, Columbia University; Assistant Radiologist, Presbyterian Hospital.

Arthur C. DeGraff, M.D., F.A.C.P., Samuel A. Brown Professor of Therapeutics, New York University College of Medicine; Visiting Physician, Bellevue Hospital.

Clarence E. de la Chapelle, M.D., F.A.C.P., Professor of Clinical Medicine, New York University College of Medicine; Visiting Physician, Bellevue Hospital.

William Dock, M.D., Professor of Medicine, Long Island College of Medicine; Chief of Medical Service, The Long Island College Hospital; Brooklyn.

A. Wilbur Duryee, M.D., F.A.C.P., Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Attending Physician, New York Post-Graduate Hospital of Columbia University.

Harry Gold, M.D., Associate Professor of Pharmacology, Cornell University Medical College; Attending Cardiologist, Beth Israel Hospital.

Ross Golden, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Director of Radiology, Presbyterian Hospital.

William Goldring, M.D., F.A.C.P., Associate Professor of Medicine, New York University College of Medicine; Associate Visiting Physician, Bellevue Hospital.

Magnus I. Gregersen, M.D., Professor of Physiology, College of Physicians and Surgeons, Columbia University.

Franklin M. Hanger, Jr., M.D., F.A.C.P., Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University; Associate Attending Physician, Presbyterian Hospital.

George H. Humphreys, II, M.D., F.A.C.S., Assistant Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University; Assistant Attending Surgeon, Presbyterian Hospital.

Thomas H. Hunter, M.D., Resident Physician, Presbyterian Hospital.

Paul Klemperer, M.D., Clinical Professor of Pathology, College of Physicians and Surgeons, Columbia University; Pathologist, Mt. Sinai Hospital.

Robert L. Levy, M.D., F.A.C.P., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Visiting Physician and Director of Department of Cardiology, Presbyterian Hospital.

Edwin P. Maynard, Jr., M.D., F.A.C.P., Professor of Clinical Medicine, Long Island College of Medicine; Chief Attending Physician, The Brooklyn Hospital.

B. S. Oppenheimer, M.D., F.A.C.P., Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Consulting Physician, Mt. Sinai Hospital.

Walter W. Palmer, M.D., F.A.C.P., Bard Professor of Medicine, College of Physicians and Surgeons, Columbia University; Director of Medical Service, Presbyterian Hospital.

Harold E. B. Pardee, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital.

Bronson S. Ray, M.D., Associate Professor of Surgery, Cornell University Medical College; Attending Surgeon, New York Hospital.

Dickinson W. Richards, Jr., M.D., Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Visiting Physician, Bellevue Hospital.

David D. Rutstein, M.D., Instructor in Medicine, College of Physicians and Surgeons, Columbia University; Associate Visiting Physician, Bellevue Hospital; Deputy Commissioner of Health, New York City.

Edith E. Sproul, M.D., Assistant Professor of Pathology, College of Physicians and Surgeons, Columbia University.

Harold J. Stewart, M.D., F.A.C.P., Associate Professor of Medicine, Cornell University Medical College; Attending Physician, New York Hospital.

Marcy L. Sussman, M.D., Assistant Professor of Radiology, College of Physicians and Surgeons, Columbia University; Radiologist, Mt. Sinai Hospital.

William C. Von Glahn, M.D., Professor of Pathology, New York University College of Medicine; Director of Pathology, Bellevue Hospital.

Harold G. Wolff, M.D., F.A.C.P., Associate Professor of Medicine, Cornell University Medical College; Attending Physician, New York Hospital.

This course is designed to give, in one week, a summary of current knowledge concerning the more important aspects of cardiovascular diseases. The speakers have been chosen because of their special interest and scientific activity in the subjects they will discuss. Clinical features will be stressed throughout; but, in addition to diagnosis and treatment, basic physiologic and pathologic mechanisms will be considered.

All sessions will be held in amphitheatres at the College of Physicians and Surgeons, Columbia University.

Luncheon may be obtained at a reasonable price at Bard Hall, which is the student dormitory, located at 50 Haven Avenue. This is within three minutes' walking distance of the College. The lunch hour will be from 1:00 to 2:00 p.m. every day except Friday, March 23, when it will be from 12:00 noon to 1:00 p.m.

Outline of Course

Monday, March 19

A.M. Session—Amphitheatre A

9:00–10:00 Introductory Remarks.
Dr. Palmer.
The Special Field of Cardiology.
Dr. Levy.

10:00–11:00 Blood Volume in Shock.
Dr. Gregersen.

11:00–12:00 Congenital Heart Disease.
Dr. de la Chapelle.

12:00– 1:00 Cardiovascular Syphilis.
Dr. Maynard.

P.M. Session—Amphitheatre A

2:00– 3:00 Public Health Aspects of Heart Disease with Special Reference to Rheumatic Fever.
Dr. Rutstein.

3:00– 4:00 Recent Studies of Peripheral Circulatory Failure.
Dr. Richards.

4:00– 5:00 The Electrocardiogram in Diagnosis and Prognosis.
Dr. Pardee.

Tuesday, March 20

A.M. Session—Amphitheatre A

9:00–10:00 Therapeutic Use of Digitalis and Quinidine in Disorders of the Heart.
Dr. Gold.

10:00–11:00 Analysis and Diagnosis of Heart Disease by Use of Catheterization of Right Heart.
Dr. Richards.

11:00–12:00 Diuretics in the Treatment of Heart Failure.
Dr. DeGraff.

12:00– 1:00 Roentgenologic Diagnosis of Cardiovascular Diseases.
Dr. Golden, Dr. Sussman and Dr. Collins.

P.M. Session—Amphitheatre A

2:00– 3:00 The Rôle of the Kidney in the Genesis of Hypertension.
Dr. Goldring.

3:00– 4:00 Coronary Heart Disease and Cardiac Pain.
Dr. Levy.

4:00– 5:00 Management of Patients with Heart Disease during Pregnancy and Labor.
Dr. Pardee.

Wednesday, March 21

A.M. Session—Amphitheatre H

9:00–10:00 Use of Sedatives in Cardiac Disorders.
Dr. DeGraff.

10:00–11:00 Cardiac Arrhythmias.
Dr. Stewart.
11:00–12:00 Rheumatic Fever and Rheumatic Heart Disease.
Dr. Hanger.
12:00– 1:00 Roentgenologic Diagnosis of Cardiovascular Diseases.
Dr. Golden, Dr. Sussman and Dr. Collins.

P.M. Session—Amphitheatre A
2:00– 3:15 Management of the Patient with Coronary Heart Disease.
Dr. Levy.
3:15– 5:00 Evaluation of Surgical Procedures in Cardiovascular Diseases: Hypertension, Cardiac Pain and the Carotid Sinus Syndrome.
Dr. Ray.

Thursday, March 22

A.M. Session—Amphitheatre F
9:00–10:00 Management of Occlusive Peripheral Vascular Disease.
Dr. Duryee.
10:00–11:00 Treatment of Hypertensive Vascular Disease.
Dr. Atchley.
11:00–12:00 Cardiac Arrhythmias.
Dr. Stewart.
12:00– 1:00 Clinical Pathological Conference on Lupus Erythematosus and Periarteritis Nodosa.
Dr. Baehr and Dr. Klemperer.

P.M. Session—Amphitheatre F
2:00– 3:00 Pathology of Rheumatic Fever and Cardiovascular Syphilis.
Dr. Von Glahn.
3:00– 4:00 Inhalation of High Concentrations of Oxygen in Coronary Sclerosis and Congestive Heart Failure.
Dr. Barach.
4:00– 5:00 Clinical-Pathological Conference.
Dr. Sproul.

Friday, March 23

A.M. Session—Amphitheatre F
9:00–10:00 Pathologic Anatomy of Arteriosclerosis and Coronary Heart Disease.
Dr. Klemperer.
10:00–11:00 Treatment of Bacterial Endocarditis with Penicillin, Heparin and the Sulfonamides.
Dr. Hunter.
11:00–12:00 Treatment and Prophylaxis of Rheumatic Fever.
Dr. Hanger.

P.M. Session—Amphitheatre H
1:00– 2:00 Diagnosis, Medical Management and Surgical Treatment of Chronic Constrictive Pericarditis.
Dr. Stewart
2:00– 3:00 Cardiac Disorders in Thyroid Dysfunction.
Dr. de la Chapelle.
3:00– 4:00 Surgical Treatment of Patent Ductus Arteriosus.
Dr. Humphreys.
4:00– 5:00 Neurocirculatory Asthenia and Related Problems.
Dr. Oppenheimer.

Saturday, March 24

A.M. Session—Amphitheatre H

9:00–10:00 Rest in the Treatment of Cardiac Conditions.
Dr. Dock.

10:00–11:00 Psychosomatic Aspects of Cardiovascular Diseases.
Dr. Wolff.

11:00– 1:00 Medical Clinic.
Dr. Palmer and Associates.

Course No. 2—Mechanics of Disease

(April 9–21, 1945)

Peter Bent Brigham Hospital and Harvard Medical School

Boston, Mass.

George W. Thorn, M.D., F.A.C.P., *Director*

(Minimal Registration, 20; Maximal Registration, 35)

Officers of Instruction

Fuller Albright, M.D., Physician, Massachusetts General Hospital; Associate Professor of Medicine, Harvard Medical School.

S. Howard Armstrong, Jr., M.D., Associate in Medicine, Peter Bent Brigham Hospital; Instructor in Medicine and Research Associate in Physical Chemistry, Harvard Medical School.

Edwin B. Astwood, M.D., Associate in Medicine, Peter Bent Bringham Hospital; Assistant Professor of Pharmacotherapy, Harvard Medical School.

Donald L. Augustine, S.D., Associate Professor of Comparative Pathology and Tropical Medicine, Harvard Medical School.

C. Cabell Bailey, M.D., Physician, New England Deaconess Hospital; Research Fellow in Medicine, Harvard Medical School.

Orville T. Bailey, M.D., Associate in Pathology, Harvard Medical School.

C. Sidney Burwell, M.D., F.A.C.P., Physician, Peter Bent Brigham Hospital; Research Professor of Clinical Medicine and Dean, Harvard Medical School.

William B. Castle, M.D., F.A.C.P., Associate Director of the Thorndike Memorial Laboratory and Director of the Second and Fourth Medical Services, Boston City Hospital, Professor of Medicine, Harvard Medical School.

Edwin J. Cohn, Ph.D., Professor of Biological Chemistry, Harvard Medical School.

Charles S. Davidson, M.D., Assistant Director of the Second and Fourth Medical Services, Boston City Hospital; Assistant in Medicine, Harvard Medical School.

Frank C. d'Elseaux, M.D., Associate in Psychiatry, Peter Bent Brigham Hospital; Instructor in Psychiatry, Harvard Medical School.

Derek E. Denny-Brown, M.D., F.R.C.P., Director of the Neurological Unit, Boston City Hospital; Professor of Neurology, Harvard Medical School.

Lewis Dexter, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Associate in Medicine, Harvard Medical School.

Louis K. Diamond, M.D., Visiting Physician, Children's Hospital; Assistant Professor of Pediatrics, Harvard Medical School.

E. Stanley Emery, M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital; Instructor in Medicine, Harvard Medical School.

John F. Enders, Ph.D., Associate Professor of Bacteriology and Immunology, Harvard Medical School.

Sidney Farber, M.D., Pathologist, Children's Hospital; Assistant Professor of Pathology, Harvard Medical School.

Cutting B. Favour, M.D., Junior Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School.

Clement A. Finch, M.D., Junior Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School.

Quentin M. Geiman, Ph.D., Assistant Professor of Tropical Diseases, Harvard Medical School.

Robert E. Gross, M.D., F.A.C.S., Associate in Surgery, Peter Bent Brigham Hospital; Associate Visiting Surgeon, Children's Hospital; Assistant Professor of Surgery, Harvard Medical School.

D. Mark Hegsted, Ph.D., Associate in Nutrition, Harvard Medical School.

John Homans, M.D., Acting Surgeon in Charge of Circulatory Diseases, Peter Bent Brigham Hospital; Clinical Professor of Surgery, Emeritus, Harvard Medical School.

Clinton v.Z. Hawn, M.D., Instructor in Pathology, Harvard Medical School.

Henry Jackson, Jr., M.D., Assistant Visiting Physician, Boston City Hospital; Assistant Professor of Medicine, Harvard Medical School.

Charles A. Janeway, M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital; Visiting Physician, Children's Hospital; Assistant Professor of Pediatrics and Instructor in Bacteriology and Immunology, Harvard Medical School.

Chester M. Jones, M.D., F.A.C.P., Physician, Massachusetts General Hospital; Clinical Professor of Medicine, Harvard Medical School.

Elliott P. Joslin, M.D., F.A.C.P., Physician, New England Deaconess Hospital; Medical Director, George F. Baker Clinic; Clinical Professor of Medicine, Emeritus, Harvard Medical School.

Thomas D. Kinney, M.D., Associate Pathologist, Peter Bent Brigham Hospital; Instructor in Pathology, Harvard Medical School.

Otto Krayer, M.D., Consulting Pharmacologist, Peter Bent Brigham Hospital; Associate Professor of Comparative Pharmacology and Head of the Department, Harvard Medical School.

Eugene M. Landis, M.D., F.A.C.P., Consulting Physiologist, Peter Bent Brigham Hospital; George Higginson Professor of Physiology, Harvard Medical School.

Samuel A. Levine, M.D., F.A.C.P., Physician, Peter Bent Brigham Hospital; Assistant Professor of Medicine, Harvard Medical School.

Arthur J. Lockhart, M.D., Assistant in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School.

F. William Marlow, Jr., M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital; Associate in Medicine, Harvard Medical School.

John M. McKibbin, Ph.D., Instructor in Nutrition, Harvard Medical School.

James H. Means, M.D., F.A.C.P., Chief of Medical Services, Massachusetts General Hospital; Jackson Professor of Clinical Medicine, Harvard Medical School.

George R. Minot, M.D., F.A.C.P., Director of the Thorndike Memorial Laboratory, Boston City Hospital; Professor of Medicine, Harvard Medical School.

Robert T. Monroe, M.D., F.A.C.P., Senior Associate in Medicine, Peter Bent Brigham Hospital; Associate in Medicine, Harvard Medical School.

William P. Murphy, M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital; Associate in Medicine, Harvard Medical School.

Francis C. Newton, M.D., F.A.C.S., Surgeon-in-Chief (Acting), Peter Bent Brigham Hospital; Assistant Professor of Surgery, Harvard Medical School.

Harlan F. Newton, M.D., F.A.C.S., Senior Associate in Surgery, Peter Bent Brigham Hospital; Associate in Surgery, Harvard Medical School.

James P. O'Hare, M.D., Physician, Peter Bent Brigham Hospital; Assistant Professor of Medicine, Harvard Medical School.

William C. Quinby, M.D., F.A.C.S., Urological Surgeon, Peter Bent Brigham Hospital; Clinical Professor of Genito-Urinary Surgery, Emeritus, Harvard Medical School.

Rulon W. Rawson, M.D., Assistant in Medicine, Massachusetts General Hospital; Instructor and Henry P. Walcott Fellow in Clinical Medicine, Harvard Medical School.

Howard F. Root, M.D., F.A.C.P., Physician-in-Chief, New England Deaconess Hospital; Associate in Medicine, Harvard Medical School.

George C. Shattuck, M.D., Consultant in Tropical Medicine, Peter Bent Brigham Hospital; Clinical Professor of Tropical Medicine, Harvard Medical School.

Richard M. Smith, M.D., Physician-in-Chief, Children's Hospital; Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School.

Reginald H. Smithwick, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

Merrill C. Sosman, M.D., Roentgenologist, Peter Bent Brigham Hospital; Clinical Professor of Roentgenology, Harvard Medical School.

Frederick J. Stare, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Associate Professor of Nutrition, Harvard Medical School.

Siegfried J. Tannhauser, M.D., Associate Chief, Pratt Diagnostic Hospital; Professor of Clinical Medicine, Tufts College Medical School.

George W. Thorn, M.D., F.A.C.P., Physician-in-Chief, Peter Bent Brigham Hospital; Hersey Professor of the Theory and Practice of Physic, Harvard Medical School.

Priscilla White, M.D., F.A.C.P., Physician, New England Deaconess Hospital; Instructor in Pediatrics, Tufts College Medical School.

S. Burt Wolbach, M.D., Pathologist, Peter Bent Brigham Hospital; Shattuck Professor of Pathological Anatomy, Harvard Medical School.

All meetings will be held in the Amphitheatre of the Peter Bent Brigham Hospital unless otherwise announced.

This course is primarily designed for internists who not only wish to keep abreast of recent developments in the field of Internal Medicine, but who are actually interested in learning newer technics in the diagnosis and treatment of disease. With this in mind, the group has been limited to a maximum of thirty-five so that adequate provision may be made for demonstrations and laboratory work.

Outline of Course

Monday, April 9

A.M. Session

9:00–12:00 Pulmonary Embolism.
Dr. Dexter, Dr. Homans, Dr. Lockhart and Dr. Sosman.

12:00– 1:00 Clinical-Pathological Conference.
Dr. Emery and Dr. Wolbach.

P.M. Session

2:00– 4:00 Bacteriological Technics; Demonstrations and Laboratory.
Dr. Favour and Dr. Janeway.

4:00– 5:00 Neurological Rounds.
Dr. Denny-Brown.

Tuesday, April 10

A.M. Session

9:00–12:00 Adrenal Disorders.
Dr. Albright and Dr. Thorn.

12:00– 1:00 X-ray Conference.
Dr. Sosman.

P.M. Session
2:00– 5:00 Blood Proteins.
Dr. Armstrong, Dr. Cohn and Dr. Janeway, with a visit to the Plasma Fractionation Laboratory.

Evening
8:15–10:00 Harvard Medical Society.

Wednesday, April 11

A.M. Session
9:00–12:00 Nutrition
Dr. Hegsted, Dr. Stare, Dr. Thorn and Associates.
12:00– 1:00 Clinical-Pathological Conference, Children's Hospital.
Dr. Farber and Dr. Smith.

P.M. Session
2:00– 5:00 Diseases of the Liver.
Dr. Armstrong, Dr. Jones, Dr. McKibben, Dr. Sosman, Dr. Stare and Dr. Thorn.

Thursday, April 12

A.M. Session
9:00– 1:00 Sulfonamide and Penicillin Therapy; Demonstrations.
Dr. Favour, Dr. Janeway and Dr. Marlow.

P.M. Session
2:00– 5:00 Diseases of the Kidney.
Dr. Dexter, Dr. O'Hare, Dr. Sosman and Dr. Thorn.

Friday, April 13

A.M. Session
9:00– 1:00 Thyroid Disorders.
Dr. Astwood, Dr. Levine, Dr. Means, Dr. Rawson and Dr. Thorn.

P.M. Session
2:00– 4:00 Peripheral Vascular Disease; Demonstrations and Laboratory.
Dr. Landis and Associates, Department of Physiology.
4:00– 6:00 Problems in Psychosomatic Medicine.
Dr. d'Elseaux.

Saturday, April 14

A.M. Session
9:00–10:00 Problems in Geriatrics.
Dr. Monroe.
10:00–12:00 Medical Grand Rounds.

Monday, April 16

A.M. Session
9:00–12:00 Cardiac Arrhythmias.
Dr. Burwell, Dr. Dexter and Dr. Levine.
12:00– 1:00 Clinical-Pathological Conference.
Dr. Thannhauser and Dr. Wolbach.

P.M. Session
2:00– 4:00 Congenital Heart Disease.
Dr. Burwell, Dr. Levine and Dr. Gross.
4:00– 5:00 Neurological Rounds.
Dr. Denny-Brown.

Tuesday, April 17
A.M. Session
9:00–12:00 Pulmonary Diseases.
Dr. Burwell, Dr. Favour and Dr. Newton.
12:00– 1:00 X-ray Conference.
Dr. Sosman.
P.M. Session
2:00– 5:00 Hypertension.
Dr. Dexter, Dr. Krayer, Dr. O'Hare and Dr. Smithwick.

Wednesday, April 18
A.M. Session
9:00–12:00 Virus Diseases.
Dr. Enders, Dr. Favour and Dr. Janeway.
12:00– 1:00 Clinical-Pathological Conference, Children's Hospital.
Dr. Farber and Dr. Smith.
P.M. Session
2:00– 5:00 Tropical Diseases; Demonstrations and Laboratory.
Dr. Augustine, Dr. Geiman and Dr. Shattuck, Department of Tropical Medicine.
Evening
8:00–10:00 Boston Society of Biologists.

Thursday, April 19
A.M. Session
9:00– 1:00 Hematology; Demonstrations and Laboratory Technics.
Dr. Diamond, Dr. Finch and Dr. Murphy.
P.M. Session
2:00– 4:00 Erythema Nodosum; Lupus Erythematosus; Polyarteritis.
Dr. Armstrong, Dr. Favour, Dr. Hawn and Dr. Sosman.
4:00– 6:00 Problems in Psychosomatic Medicine.
Dr. d'Elseaux.

Friday, April 20
A.M. Session
9:00– 1:00 Diabetes Mellitus.
Dr. C. C. Bailey, Dr. O. T. Bailey, Dr. Joslin, Dr. Root, Dr. Thorn and Dr. White.
P.M. Session
2:00– 5:00 Disorders of the Blood.
Dr. Castle, Dr. Davidson, Dr. Jackson and Dr. Minot.

Saturday, April 21
A.M. Session
9:00–10:00 Gout.
Dr. Thorn.
10:00–12:00 Medical Grand Rounds.

War-Time Graduate Medical Meetings

Region No. 1 (Maine, New Hampshire, Vermont, Massachusetts) and Region No. 2 (Connecticut, Rhode Island—New England Committee for War-Time Graduate Medical Meetings—Dr. W. R. Ohler, Chairman; Dr. L. E. Parkins, Secretary; Dr. S. B. Weld, Dr. A. M. Burgess, Dr. C. S. Keefer, Dr. F. T. Hill, Dr. J. P. Bowler, Dr. B. F. Cook, Executive Committee members.

Station Hospital, Dow Field, Bangor, Maine
March 20. The Skin.

Dispensary, U. S. Naval Air Station, Brunswick, Maine
March 15. Head, Spine and Nerve Injuries.

Station Hospital, Fort Williams, Portland, Maine
March 15. Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases.

Station Hospital, Presque Isle, Maine
March 15. Contagious Diseases and Complications.

Station Hospital, Grenier Field, Manchester, New Hampshire
March 14. Pilonidal Sinus and Common Diseases of the Anus and Rectum.

U. S. Naval Hospital, Portsmouth, New Hampshire
March 15. Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation.

Boston Area Station Hospital, Waltham, Massachusetts
March 15. Burns and Reconstruction Surgery.

U. S. Naval Hospital, Chelsea, Massachusetts
March 15. The Use of Penicillin and the Sulfa Drugs.

Lovell General Hospital, Fort Devens, Massachusetts
March 15. Diarrheal Diseases.

Station Hospital, Camp Edwards, Massachusetts
March 15. Stomach, Biliary Tract, Intestinal Disorders.

Cushing General Hospital, Framingham, Massachusetts
March 15. Chest and Abdominal Injuries.

Station Hospital, Camp Myles Standish, Taunton, Massachusetts
March 15. The Psychoneuroses and Their Management.

U. S. Marine Hospital, Brighton, Massachusetts
March 15. The Pneumonias and Other Respiratory Infections.

Station Hospital, Westover Field, Chicopee Falls, Massachusetts or U. S. Naval Convalescent Hospital, Springfield, Massachusetts
March 15. Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation.

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island
March 15. Fractures of Extremities.

U. S. Naval Hospital, Newport, Rhode Island
March 15. Joint Injuries.

Station Hospital, Bradley Field, Windsor Locks, Connecticut
March 15. The Pneumonias and Other Respiratory Infections.

Station Hospital, Fort H. G. Wright, Fishers Island, New York
March 15. Acute Infections of the Central Nervous System.

Region No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

Induction Center, Grand Central Palace, New York, New York
February 16. Head Injuries—Dr. Eli Jefferson Browder.

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

U. S. Naval Hospital, Philadelphia, Pennsylvania

February 23. The Esophagus and Its Diseases—Dr. L. H. Clerf.
March 23. Surgical Technic in Acute Appendicitis—Dr. George Muller.

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. C. B. Conklin.

Newton D. Baker General Hospital, Martinsburg, West Virginia

February 19. Treatment of Patients with Paraplegia Due to War Injuries—Dr. Donald Munro.
Liver Diseases Seen in the Present War—Dr. Wallace Yater.
March 5. Diagnosis and Treatment of Cardiovascular Conditions Peculiar to Military Life—Dr. Louis Hamman.
Penetrating Wounds of the Abdomen.
March 19. Experiences with Malaria—Colonel Paul F. Russell.
Diagnosis of Diarrheal Diseases—Lieutenant Colonel Hardy Kemp.

Station Hospital, Fort Belvoir, Virginia

February 26. Skin Eruptions of the Eczema Group—Dr. Walter O. Teichmann.
March 12. General Principles of Plastic Surgery—Dr. Robert E. Moran.
March 26. Seasonal Hay Fever—Dr. Grafton Tyler Brown.

A.A.F. Regional Hospital, Langley Field, Virginia

February 23. Internal Medicine.
Neurology and Neurosurgery.
March 30. Psychiatry—Dr. R. Finley Gayle.
Orthopedic Surgery.

REGION No. 8 (Western Pennsylvania, Ohio)—Dr. C. A. Doan, Chairman; Dr. P. G. Smith, Dr. F. M. Douglass.

Crile General Hospital, Cleveland, Ohio

February 27. Technic of Closure of Colostomies—Dr. Thomas E. Jones.
March 27. Problems in the Diagnosis and Management of Coronary Artery Disease—Dr. R. W. Scott.

Air Base Hospital, Patterson Field, Dayton, Ohio

February 21. Diagnosis and Surgical Treatment of Acute Cholecystitis—Dr. George Heuer.

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M. Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

Station Hospital, Truax Field, Wisconsin

February 28. Heart Disease—Dr. Chester M. Kurtz.
March 14. Arthritis—Dr. Milton C. Borman.
March 28. Peripheral Vascular Diseases—Dr. Geza de Takats.

Gardiner General Hospital, Chicago, Illinois

February 21. Present Status of Medical Planning—Dr. Morris Fishbein.
February 28. Plexus and Peripheral Nerve Injuries.
March 7. Relationship between Deficiency Diseases and the Gastro-Intestinal Tract—Dr. Clifford Barborka.

March 14. Dermatological Diseases.
March 23. Sequelae of Head Injuries—Dr. Paul Bucy.
March 28. Burns and Plastic Surgery.

Station Hospital, Fort Sheridan, Illinois

February 28. Burns and Plastic Surgery.
March 14. Malignancies in the Army Age Group—Medical X-ray and Surgical Diagnosis and Treatment.
March 28. Endocrinology.

Mayo General Hospital, Galesburg, Illinois

February 28. Endocrinology.
March 14. Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.
March 28. Psychosomatic Medicine.

Vaughan General Hospital, Illinois

February 28. Psychosomatic Medicine.
March 14. Wound Healing and Tendon Surgery.
March 28. Mental Hygiene and the Prevention of Neuroses in War.

Station Hospital, Camp Ellis, Illinois

February 28. Mental Hygiene and the Prevention of Neuroses in War.
March 14. Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.
March 28. Peptic Ulcer, Gall Bladder and Liver Diseases.

Station Hospital, Chanute Field, Illinois

February 28. Diseases of the Kidneys—Urogenital Tract.
March 14. Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment.
March 28. High Blood Pressure.

Billings General Hospital, Fort Benjamin Harrison, Indiana

February 28. High Blood Pressure.
March 14. Brain and Spinal Cord Injuries.
March 28. Conditions Affecting Glucose Metabolism.

Wakeman General Hospital, Camp Atterbury, Indiana

February 28. Conditions Affecting Glucose Metabolism.
March 14. Plexus and Peripheral Nerve Injuries.
March 28. Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care.

REGION No. 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr. F. D. Dickson, Chairman; Dr. O. P. J. Falk, Dr. H. H. Turner.

Station Hospital, Rosecrans Field, St. Joseph, Missouri

March 15. General Surgery.
Venereal Diseases and Urology.

Regional Hospital, Fort Riley, Kansas

March 15. General Surgery.
Shock, Burns and Blood Derivatives.
March 29. Chest Surgery.
Diseases of the Blood.

Winter General Hospital, Topeka, Kansas

February 22. Plastic and Maxillary Surgery—Dr. Earl C. Padgett.
Clinical Psychiatry—Dr. G. Leonard Harrington.

SPECIAL NOTICES

Announcement of the Spring Refresher Course in Otolaryngology by the University of Illinois College of Medicine

The 5th semi-annual refresher course in laryngology, rhinology and otology will be conducted by the University of Illinois, College of Medicine at the College in Chicago, March 26 to 31 inclusive, 1945. Although the course will be largely didactic, some clinical instruction will be included. This course is intended primarily for ear, nose and throat specialists. As the registration is limited to thirty, applications will be considered in the order in which they are received. The fee is $50.00. When writing for application please give details concerning school and year of graduation, and past training and experience.

Address—Dr. A. R. Hollender, Chairman, Refresher Course Committee, Department of Otolaryngology, University of Illinois, College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

OBITUARY

DR. FREDERICK GEORGE SPEIDEL

Dr. Frederick George Speidel, F.A.C.P., Louisville, Kentucky, died suddenly of heart disease on October 15, 1944.

Dr. Speidel was born on March 14, 1889. He received his Medical Degree in 1917 from the University of Louisville School of Medicine, and in his later career pursued postgraduate study at the U. S. Naval Medical School, Rockefeller Institute for Medical Research, and the University of Michigan. During World War I and immediately thereafter he served for a time as instructor in Clinical Chemistry at the U. S. Naval Medical School. Thereafter he was Assistant in Medicine (1919–1922), instructor in Therapeutics (1922–1923), clinical instructor in Pharmacology (1923–1935), and assistant clinical professor of Pharmacology (since 1935) at his alma mater. For many years he was a member of the staff of the Kentucky Baptist, St. Anthony's, and Kosair Crippled Children's Hospitals and the Norton Memorial Infirmary.

Dr. Speidel had served as Secretary-Treasurer, First and Second Vice-Presidents of the Jefferson County Medical Society, and also as Secretary-Treasurer and President of the Society of Physicians and Surgeons. He was a member of the Kentucky State Medical Association and the Southern Medical Association; a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1938. He was a diplomate of the American Board of Internal Medicine, and the author of numerous published papers.

Dr. Speidel was one of the outstanding internists of Louisville, and was extremely popular with his patients and with the entire medical profession. He felt with so many physicians absent from the community that he could carry on in spite of everything, and it is generally believed by his friends that this added strain was responsible for his very sudden death from coronary thrombosis.

C. W. Dowden, M.D., F.A.C.P.,
Governor for Kentucky

ABSTRACTED AND ABRIDGED MINUTES

BOARD OF REGENTS

PHILADELPHIA, DECEMBER 16, 1944

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters, Philadelphia, December 16, 1944, with President Ernest E. Irons presiding. Fifteen members of the Board were in attendance.

The Executive Secretary read abstracted minutes of the preceding meeting of the Board and presented numerous communications, none of which required special action other than the following:

1. A resolution was adopted, discouraging a recently organized medical society from scheduling its meetings at the same time and with the meeting of the American College of Physicians.
2. It was unanimously voted to continue the Conference Committee on Graduate Training in Medicine to confer and work with a similar Committee from the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. The following appointments were made by President Irons to serve on this Committee:

   Dr. Reginald Fitz, Boston.
   Dr. LeRoy Sloan, Chicago.

The Secretary General, Dr. George Morris Piersol, read a list of the deaths of 47 Fellows and 5 Associates since the preceding meeting of the Board. Included within the list were the names of Dr. Charles Hartwell Cocke, Asheville, N. C., First Vice President of the College, and Dr. William B. Breed, Boston, Mass., Chairman of the Board of Governors. At the request of the Chairman, the Board arose and stood in silence in respect to those deceased.

Dr. Piersol then reported for record in the minutes, the names of 24 additional Life Members who had subscribed to the Endowment Fund of the College since the preceding meeting of the Board of Regents.

As Chairman of the Committee on Credentials, Dr. Piersol proceeded with the report of that Committee: "I would like to remind the Regents that the Credentials Committee, in the past few months, has suffered serious catastrophies in the deaths of Dr. Charles Hartwell Cocke and Dr. William B. Breed, who died within a short time of each other, leaving two vacancies on this Committee of six. Particularly do I want to mention these men and to pay a tribute to them personally for the long years of arduous and enthusiastic work which they performed. The Committee deeply regrets the loss of these active and efficient men."

"The Credentials Committee met yesterday and reviewed a large number of candidates. An analysis of the recommendations of the Committee is as follows:

A. Candidates for Fellowship.

Recommended for advancement from Associateship ...	105	
Recommended for direct election	23	128

Recommended for election first for Associateship	16
Deferred	32
Rejected	18
Total number of candidates for Fellowship	194

B. Candidates for Associateship.

Recommended for election	167
Deferred	33
Rejected	22
Total number of candidates for Associateship	222"

At this point, mimeographed lists of the candidates for Fellowship and Associateship were passed to each Regent for survey. Formal resolutions were adopted electing 128 candidates to Fellowship and 183 candidates to Associateship (these names were published in the News Notes section of the January, 1945, Issue of this journal).

On the recommendation of the Credentials Committee, the term of Associateship was extended beyond the customary five-year maximum for 26 Associates now on military service; the names of five Associates not on military service, who had failed to qualify for advancement to Fellowship within the five-year period, were dropped from the Roster.

An analysis of the group of candidates elected to Associateship on December 17, 1939, five years previous to this meeting, is as follows:

Advanced to Fellowship	114	(77 %)
Deceased	3	
Dropped for failure to take up election	1	
Dropped for failure to qualify for Fellowship	5	
Associate term extended because of military service	26	
	149	

On recommendation of the Committee on Credentials, Dr. William R. Vis, Grand Rapids, Mich., was re-instated to active Fellowship in the College. On recommendation by the Committee on Credentials, the Board of Regents approved that areas, such as New York City, Brooklyn and other comparable communities may, on selection by the local Governor, have a consulting committee of five or six Fellows by whom all proposals will be reviewed before endorsement by the Governor, for recommendation to the Committee on Credentials.

Commenting on candidates presented for direct Fellowship in the College, Dr. Piersol said, "It is astonishing how many men without any adequate qualifications are being proposed for direct election to Fellowship. The Regents and Governors need to do some missionary work in this direction. The credentials of those the Committee recommended for direct Fellowship were scrutinized with unusual care, and those selected represent outstanding men in the field of internal medicine and have the necessary qualifications to justify their election. However, at least 16 of the candidates proposed for direct election were first recommended for election to Associateship and several other candidates for direct election were rejected."

"The Credentials Committee again has the temerity to recommend to the Board of Regents that certification be made a prerequisite for Associateship, rather than merely for advancement to Fellowship, and, if approved, that the Committee shall be authorized to draw up proper wording for this change in the regulations. As you know, since April 6, 1940, advancement to Fellowship requires certification by the national board in any specialty where such a board exists. The Committee is

now seeking some further definite yardstick by which they can measure a man's professional ability. The Committee has felt for a long time that the present method is inadequate, uncertain and sometimes unjust. If this change in requirements is adopted, let the Associate term then be devoted to a demonstration of the candidate's competency, scientific attainments and other contributions. As a matter of fact, many of the present candidates for Associateship are already certified and many of them have the idea that certification is all that is necessary to become a Fellow, which, of course, is wrong. The present system is not entirely satisfactory; if candidates are required to be certified before becoming Associates, they will then realize that to become a Fellow they have to do something more, which should be a stimulus and should elevate Fellowship to a higher plane."

There was extended discussion of the matter among members of the Credentials Committee and the members of the Board of Regents and opinions were in some cases divergent. On motion by Dr. Piersol, seconded by Dr. Fitz, and regularly carried, it was resolved that this matter should be placed on the agenda at the next joint meeting of the Board of Regents and Board of Governors. During the discussion of this motion, it was revealed that at the present time, certification is a minimum professional requirement for advancement to Fellowship, but that the Credentials Committee will not accept certification as the sole professional requirement for Fellowship; the Committee emphasizes the need of some productivity, such as publications, a thesis or other material, with definite consideration given to appointments, maturity, reputation and standing. A Fellow of the College must be something more than just a good doctor who is certified. He must be an internist or a specialist in an allied specialty, who is able to take part in the scientific aspects of his specialty and demonstrate his fitness and interest in that specialty. Fellowship must be looked upon as a definite and distinct honor, that stamps a man not only as a good internist, but as an outstanding one.

Dr. James E. Paullin, Chairman of the Committee on Constitution and By-laws, reported that two matters had been submitted to the Committee for consideration for amendments to the By-laws:

1. The By-laws should provide for the Board of Governors, similarly as it provides for the Board of Regents, some limitation for the term of office.
2. A change in the method of appointing the Nominating Committee.

After extensive discussion, the following resolutions were adopted:

1. RESOLVED, that a proper By-law be prepared providing for the limitation in the term of office of members of the Board of Governors to two consecutive terms of three years each, and that this By-law be presented for adoption at the next annual business meeting in the spring of 1945.
2. RESOLVED, that inasmuch as the present provision for the nomination and election of Officers, Regents and Governors is wholly democratic and has worked satisfactorily and well ever since the adoption of the present By-laws, no change shall be recommended.

Dr. Walter W. Palmer, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, presented a report for that Committee, making the observation that the income from the journal is at present very largely responsible for much of the surplus of the College, because of large orders received from the Army and Navy for distribution to medical installations all over the world. The Regents gave approval for the Army Medical Library to reproduce material from the ANNALS for use during the

war. A request from a publishing concern in Brazil for permission to translate the ANNALS into Portuguese, but to utilize the new publication in their country for their own advertising and aggrandizement, was refused.

Dr. Paul Clough, as Editor, reported primarily on the acquisition of material for publication in the ANNALS and the preparation of book reviews. There had been a definite, gradual falling off in the number of acceptable articles for publication in the ANNALS. Many speakers during the war have found inadequate time to prepare manuscripts, and frequently speak extemporaneously; such papers have not been available in many instances for publication. Dr. Clough reported that he had not been able to give much time personally to the matter of writing book reviews, and most of the reviewers who had done this for the ANNALS in the past, are now on active military duty. He suggested no remedy for the present shortage of reviews. On the recommendation of Dr. O. H. Perry Pepper, Chairman of the Finance Committee, an additional appropriation was made available to the Acting Editor to enable him to attend in person more of the regional meetings of the College in pursuit of suitable presentations for publication in the ANNALS. The opinion was expressed in discussion that the College has allowed possibly too much of the material that appears in the ANNALS to be derived from its meetings where it is unlikely, especially at the regional meetings, for new work to be announced for the first time. It would be a marked improvement if a greater effort might be made to obtain for the ANNALS more of the new papers covering new discoveries, new reports and new advances.

The Executive Secretary, Mr. Loveland, was called upon to make a report for the Committee on Educational Policy and the Advisory Committee on Postgraduate Courses.

MR. LOVELAND: All members of the Committe on Educational Policy are absent, and the Chairman of the Advisory Committee on Postgraduate Courses, Captain Bortz, is in the Pacific. Consequently, no meeting of this Committee could be held yesterday.

Your Executive Secretary has carried on this work, with consultation with the members of the Advisory Committee on Postgraduate Courses, and submits the following report:

I. Spring, 1944, Courses: (Total Registration, 407)
- Course No. 1, *General Medicine,* University of Michigan, Dr. C. C. Sturgis, Director, (April 10–15).
- Course No. 2, *Clinical Medicine with Special Emphasis upon the Hematologic Viewpoint,* Ohio State University, Dr. Charles A. Doan, Director, (April 17–22).
- Course No. 3, *Internal Medicine,* Massachusetts General Hospital, Dr. James H. Means, Director, (April 24–29).

The above courses were reported upon by Captain Bortz at the Chicago meeting of this Board on April 1.

II. Autumn, 1944, Courses: (Total Registration, 447)
- Course No. 1, *Cardiology,* Massachusetts General Hospital, Dr. Paul D. White, Director, (October 2–7).
- Course No. 2, *General Medicine,* University of Oregon, Dr. Homer P. Rush, Director, (October 9–14).
- Course No. 3, *Internal Medicine,* University of Minnesota, Drs. William A. O'Brien, Cecil J. Watson and E. H. Rynearson, Directors, (October 9–14).
- Course No. 4, *Allergy,* Roosevelt Hospital, New York City, Dr. Robert A. Cooke, Director, (October 16–21).

Course No. 5, *Internal Medicine*, Chicago Institutions, Dr. Willard O. Thompson, Director, (October 23–November 4).

Course No. 6, *Special Medicine*, Philadelphia Institutions, Dr. Thomas M. McMillan, Director, (December 4–15).

We were gratified at being able to successfully put on for the first time one of our courses on the West Coast. Dr. Rush, with his associates, including Dr. Coffen, did an exceedingly fine job. Those taking the courses were highly pleased and many letters of appreciation were received. We predict that now that we have successfully established a beginning on the West Coast, the demand for courses there will increase.

Dr. White's course in Cardiology, while intended to be limited to 50, grew to 71, and more than one hundred applicants had to be turned away. There was an urgent request for the repetition of this course this coming winter or spring, but Dr. White was so exhausted that he has asked to have the repetition of the course delayed at least until the autumn of 1945.

The course in Internal Medicine at the University of Minnesota was up to its usual standard, but the demand was not as great for the course this autumn as it had been on previous occasions. However, there was a very satisfactory registration, and those in attendance were highly pleased with the course.

Course No. 4, Allergy, by Dr. Cooke, which has been given several times previously, had the largest registration this year in its history. Dr. Cooke always puts on a fine course and is recognized the country over as one of our finest teachers in the field of Allergy.

Course No. 5 in Internal Medicine at Chicago Institutions was held in Thorne Hall, Northwestern University, and had the active interest and support of all our Officers and members in Chicago. The course was intended to be limited to 60, but the Director, Dr. Thompson, was enthusiastic about accommodating all comers. The result was that there was a total registration of 179 different individuals; however, 70 of these were part-time registrants. Enough cannot be said for Dr. Thompson's enthusiasm and his capacity for hard work and fine organization. He telephoned us at all times of the day and night; he telegraphed frequently and wrote scores of letters; he was ably assisted especially by Governor Walter L. Palmer, President Irons and Regent Sloan. The course terminated in a Regional Meeting, which was second to none that had been held in the country. The only question that some have raised is whether or not we should encourage such large classes, although in this particular instance the course was purely didactic, and none suffered, other than from the standpoint of the inability to become intimately acquainted with other members of the class. However, the Chicago Officers attempted to remedy this to a degree by some really extensive entertaining of the group as a whole.

Course No. 6, Special Medicine, at Philadelphia, terminating with a Regional Meeting of this territory yesterday, was, we believe, an excellent course and well received. Dr. McMillan, and his faculty from various Philadelphia Institutions, worked faithfully in an attempt to give the class the best available in Philadelphia at the present time. Instead of holding the class at various institutions, as was done a year ago, with a certain amount of confusion among those unfamiliar with our transportation system, all classes were held at the Philadelphia General Hospital. The registration for this course was not as great as a year ago, but War conditions, including transportation and hotel facilities, interfere more now and, anyhow, it has been observed that the same course, repeated too frequently, does not call forth the same number of registrants each succeeding year. The law of supply and demand is always evident. Some variation in the courses, the institutions and the directors from time to time meets with greater demand than the repetition of the same course too frequently.

From the reports handed to you, you will note that the total registration for the

autumn courses amounted to 447, making a total registration for the year of 854.

III. Proposed Courses for late winter and spring, 1945:

Course No. 1, *Cardiology,* College of Physicians and Surgeons, Columbia University, New York City, Dr. Robert L. Levy, Director, (March 19–24).

Course No. 2, *Mechanics of Disease,* Harvard University and Peter Bent Brigham Hospital, Dr. George W. Thorn, Director, (April 9–21).

Course No. 3, *Clinical Medicine with Special Emphasis upon the Hematologic Viewpoint,* Ohio State University, Dr. Charles A. Doan, Director, (April 16–21).

Course No. 4, *Gastrointestinal Diseases,* Graduate Hospital, Philadelphia, Dr. Henry L. Bockus, Director, (April 23–28).

Course No. 5, *Applications of Psychiatry to the Practice of Internal Medicine,* University of Wisconsin, Dr. Hans Reese, Director, (April 30–May 5).

The last course has great possibilities of being both practicable and interesting if properly organized and conducted. Much interest in such a course has been expressed by members of the College.

One of our great problems, of course, is being able to organize faculties and obtain facilities under present conditions. I am sure the Advisory Committee on Postgraduate Courses will appreciate such suggestions, instructions or approval as the Board of Regents may be willing to offer.

(President Irons requested the Executive Secretary to present also a report on the regional meetings.)

MR. LOVELAND: For the current calendar year 1944, the following meetings have been held:

1. SOUTHERN CALIFORNIA, at Los Angeles, February 26.
2. MONTANA and WYOMING, at Great Falls, Mont., May 6.
3. MISSISSIPPI, at Jackson, May 9.
4. COLORADO, UTAH, ARIZONA, NEW MEXICO, KANSAS and NEBRASKA, at Denver, June 22–24.
5. IDAHO, OREGON, WASHINGTON, ALBERTA, BRITISH COLUMBIA, MANITOBA and SASKATCHEWAN, at Vancouver, B. C., September 14–15.
6. STATE OF NEW YORK, at New York City, October 20.
7. NEBRASKA and adjacent territory, at Omaha, in conjunction with War-Time Graduate Medical Meetings and the Omaha Mid-West Clinical Society, October 26–27.
8. STATE OF NORTH CAROLINA, at Chapel Hill, November 3.
9. ILLINOIS, INDIANA, IOWA, KENTUCKY, MICHIGAN, MINNESOTA, and WISCONSIN, at Chicago, November 4.
10. WESTERN PENNSYLVANIA, OHIO and WEST VIRGINIA, at Pittsburgh, November 11.
11. EASTERN PENNSYLVANIA, NEW JERSEY and DELAWARE, at Philadelphia, December 15.

Your President, your President-Elect and your Executive Secretary have been in attendance at one or more of the larger and more important of these meetings. Programs have uniformly been of high caliber, and attendance has been gratifying. Especially great enthusiasm was expressed for the meetings at Denver (a three-day meeting in conjunction with War-Time Graduate Medical Meetings), Vancouver (where we obtained the famous Dr. Wassell as one of the guest speakers), and Chi-

cago. Several of these Regional Meetings were the first ones of the character in their territory, such, for instance, as the meeting in Vancouver, the meeting in Denver and the meeting in New York. The meetings, as you already know from copies of programs sent you, have taken many forms, and we have been able to entertain a very large number of Medical Officers from the Armed Forces and a large percentage of our members.

Planned for the immediate future are the following:

1. TENNESSEE, MISSISSIPPI, LOUISIANA, ARKANSAS and EASTERN TEXAS, at Memphis, under Dr. Wm. C. Chaney, Governor for Tennessee, January 25–26, 1945.
2. OKLAHOMA, KANSAS, MISSOURI and WESTERN TEXAS, at Oklahoma City, under Dr. Lea A. Riely, Governor for Oklahoma, February 22–23, 1945.

Under course of organization, or consideration, are Regional Meetings in St. Louis, some city in New England, some city in the Middle Atlantic States and some city in the Southeastern Atlantic States.

The Regional Meeting in St. Louis will be discussed under another item on the Agenda for today, with a view to holding our Annual Business Meeting there in conjunction with the Regional Meeting, similar to the plan we followed last April in Chicago.

We confidently feel that these Regional Meetings continue to make a real contribution during the War, but the membership-at-large, in a great many instances, is looking forward to the time when we shall resume our Annual Sessions.

PRESIDENT IRONS: The report will be received with thanks.

DR. STRONG: I believe the Regional Meeting in Vancouver was a good thing for the American College of Physicians—it was a good opportunity to bring to the attention of the profession in Western Canada the valuable service that this College was rendering. Because of lack of knowledge, there is often a certain lack of interest in the College, and I think meetings of this sort will quickly dispel that lack of knowledge and there will be a tremendous increase in the activities of our College in Western Canada.

DR. BARR: The Vancouver meeting was truly an inspiring meeting and thanks to Dr. Strong's leadership, I feel that the American College of Physicians is launched in a very big way in that district.

PRESIDENT IRONS: The Chicago Regional Meeting and Postgraduate Course were extremely successful. The College is distinctly on the medical map of Chicago.

. . . . . .

On resolution by Dr. Stroud, seconded by several and unanimously carried, it was resolved that the Board of Regents convey to the Directors of the Postgraduate Courses and the General Chairman of the Regional Meetings, a vote of thanks and appreciation.

Dr. Frank Borzell, Chairman of the Committee on War-Time Graduate Medical Meetings, reported on the activities of that Committee. In the statistical review of activities, Dr. Borzell recorded that there had been 89 individual meetings, 90 continuation courses, 179 War-Time Graduate Medical Meetings and 831 daily sessions. Meetings had been conducted in 16 civilian institutions, 21 Naval installations and 102 Army installations. The total receipts for the year, $27,498.43, and the total expenditures (estimated for December), $24,737.87. Dr. Borzell pointed out the difficulties of preparing a detailed budget for the year 1945, due to uncertainty concerning the continuation of hostilities, but recommended that each contributing organization, the American College of Physicians, American Medical Association and the American College of Surgeons appropriate on the same basis as for 1944. He stated that the Committee on War-Time Graduate Medical Meetings is prepared to

render whatever assistance may be required by the Surgeons General to augment the teaching personnel at the various military installations for refresher courses planned for medical officers about to be discharged from service.

Dr. Francis Blake, Chairman of the Committee on Fellowships and Awards, reported that all activities of the Committee have been in abeyance during the war by direction of the Board of Regents. Since a year ago, the Committee had received two follow-up reports on publications by Dr. James Hopper, Jr., a former research fellow. While there had been no meeting of the Committee, the Chairman expressed the opinion that it might be advisable to give consideration to renewal of the fellowship program beginning in the autumn of 1945, with sending out notices of fellowships, perhaps in relation to providing opportunities for men returning from the services. Dr. Blake said he would consult other members of the Committee and bring in another report with definite recommendations at the spring meeting of the Board.

Dr. Reginald Fitz, Chairman of the American Board of Internal Medicine, reported that the Board had lost two valuable members during the past year, Dr. Ernest Irons, its former Chairman, and Dr. Frederic M. Hanes, resigned. The Board had examined 633 individuals during the year by written examination, 269 during February and 364 during October. A little over 200 candidates had taken the oral examinations, 57 of whom had been examined by special arrangements outside of the regular meetings, and 54 of these were examined under Colonel William Middleton's guidance in the European Theater of the War. The mortality rate had been about the same as heretofore. Fifteen per cent failed the written examinations and of those taking the oral examinations, about the same percentage of failures occurred, except in the case of men examined in the European Theater, where the percentage of failures was considerably greater. Dr. Fitz reported that 3,526 physicians have been certified, that the number of men considered for certification without examination is being rapidly decreased and that the number of men taking examinations is continuing to grow. The sub-specialty boards were working, on the whole, well, except there are some groups in specialties who have wanted to form their own boards. This is being discouraged. Dr. Fitz said the Board had adequate funds with which to work, both during the present and the future. The Board will require some new appointees by the College in the spring—one to take Dr. Hanes' place, and others to fill vacancies caused by expiring terms. It was further pointed out that the Board would desire to know the time and place of the annual meeting of the College in the spring of 1945, so that oral examinations could be arranged and scheduled.

There followed a discussion of the method of additional certification in the sub-specialties. It was explained by various members of the American Board that all candidates must pass the regular written examination and part of the regular oral examination, following which they may be admitted to the special examinations in the sub-specialties.

Dr. James E. Paullin, Acting Chairman of the Committee on Public Relations, presented the following resignations which were accepted:

Lt. Col. John B. Grow, (MC), USA, (Associate).
Dr. Virginia Hale (Associate), Gales Ferry, Conn.
Dr. Claire E. Healey (Associate), Elgin, Ill.
Dr. George H. Hess, F.A.C.P., Uniontown, Pa.

Dr. Herbert A. Burns, F.A.C.P., Minneapolis, Minn., was discontinued on the Roster, and Dr. Clayton E. Royce, F.A.C.P., Jacksonville, Fla., was accorded waiver of dues because of ill health and retirement from practice.

DR. PAULLIN (Continuing his report): The Committee received a lengthy series of resolutions from the Illinois State Medical Society concerning the support of the Miller Bill, which was introduced in Congress and which had to do with the de-

ferment of qualified pre-medical students over the age of 18, in order that the quota of medical students in our colleges could be maintained after the year 1945. Only about 60 per cent of the students in schools will be in the V–3 or V–12 program after 1945, and that will leave 40 per cent of vacancies in most schools. The Miller Bill is an effort to get Selective Service to defer approximately 6,000 men a year for the study of medicine. This has been taken up very actively by the American Medical Association, the Council on Medical Education and Hospitals and various other organizations. Your Committee thinks it would meet with a sufficient amount of action if the Board of Regents approve the resolution. I so move.

DR. STRONG: I second the motion.

GENERAL MORGAN: I have no very firm convictions about this. I have not heard of the Miller Bill before, but I question the advisability of our College going into matters that have to do with governmental policy. It probably would be a mistake, in my opinion, for this College to project itself into things concerning organized medicine of that type. The American Medical Association and the State Societies give an outlet for expression, and I doubt if the College, by and large, should enter into a matter of this kind. I think the College would do well to stick to professional matters.

DR. SLOAN: I am inclined to think that we should act as individuals rather than as a College.

DR. PAULLIN: It is only a question of providing students for the study of medicine and care of the civilian population. The Army and Navy have as many doctors as they need, and the poor civilians have very few and no chance of getting more after 1948. Practically every other organization has approved this Bill and it is more or less immaterial whether the College does or not.

GENERAL MORGAN: I might just elaborate on what I was thinking. I believe the strength of the College lies in its manifest mission of doing all that it can do to elevate the standards of the practice of medicine. Those organizations that stick to their knitting get along, by and large, better than those that let themselves be drawn into other things.

(The motion was put to vote and lost by one vote.)

DR. PAULLIN: Your Committee has a communication from Dr. Chauncey D. Leake, Vice President and Dean of the University of Texas. He requests that this College become interested in promoting and maintaining the best possible standards for hospital pharmacies; that pharmacies in hospitals should have a capable pharmacist in charge and become a center for chemical consultation throughout the hospital, and might be responsible not only for the manufacture, distribution and dispensing of various drug preparations, but also for solutions, laboratory reagents and sterile supplies. The Committee expresses sympathy with Dr. Leake's point of view, but feels that this is not within the province of the College and moves that this recommendation be adopted.

(The motion was seconded and unanimously carried.)

DR. PAULLIN: We shall refer an inquiry from a Richmond, Va., physician concerning obstetrical privileges granted doctors at a local hospital, to the American College of Surgeons.

Dr. Walter W. Palmer, Chairman of the Committee on Post-War Planning for Medical Service, reported that the Central Committee had several meetings since the last meeting of the Board of Regents and that proceedings of these meetings have been reported in the Journal of the American Medical Association. The chief items of interest had been reports from time to time by Colonel Harold C. Lueth, Liaison Officer of the Surgeon General's Office with the Council on Medical Education and Hospitals. A questionnaire was sent to every man in the service, Army, Navy and Public Health Service, asking what he would like to do after the war

and what training he desired. 20,000 replies have been received and classified; younger men want more resident work and longer training; older men want more refresher courses. In the resident and special training group, surgeons by far outweigh all others; internal medicine is second; obstetrics and gynecology is third. Requests for long-term training in surgery are going to be far beyond the facilities this country is able to supply. Another questionnaire is being prepared to determine the possibility of increasing the facilities of the country for internships, residencies and other special training. The previous calculation has been that most worthy men could be accommodated, if present opportunities could be doubled and if demobilization takes place not too rapidly. Dr. Palmer also reported that the Committee has been compiling lists from medical schools of essential teachers, key men, that they desire to have released early from military duty. This particular work is being done through the Association of American Medical Colleges. 53 schools have reported the names of 403 from the Army and 109 from the Navy, which is 8 per cent of medical officers in the Army and 2 per cent of those in the Navy. The list will be passed through the Office of Procurement and Assignment, and the Committee will collaborate with that agency.

Dr. Palmer reported also that a sub-committee of the Committee on Post-War Planning, consisting of Father Schwitalla, Dr. Frederick Coller and himself, had spent a day visiting the Veterans Administration to study the possibilities of organizing residencies of a caliber suitable for postgraduate work. Clinical material is ample, but the possibility of organizing anything that would be acceptable is still uncertain. A conference had also been held in Washington with Mr. Harold V. Sterling, who will probably administer the GI Bill. It is apparent that the Bill will be interpreted broadly with every effort to help every man coming out of the Service. Medical men will be able to get subsistence at the rate of $50.00 per month if single, $75.00 per month if married, and $500.00 per school year for training. Hospitals will probably be acceptable institutions of training.

Dr. Palmer stated that the Committee had also explored war surpluses and their post-war distribution. The National Research Council's Committee on Essential Drugs and Medical Supplies, of which Dr. Palmer is Chairman, made certain recommendations to the Senate Committee before the law was passed.

Dr. Palmer said another item considered by the Committee is a recommendation concerning the granting of temporary licenses by State Boards. The Committee has approved of such recommendation, but because it was not restricted to men in Service, as they were demobilized, several objections had been raised by various medical boards, with the result that the Committee recommended modification, restricting the granting of temporary licenses to men in Service or to men as they get out of Service, providing State Boards agree.

Dr. O. H. Perry Pepper presented the report on the Committee on Finance, making the following points:

> The income of the College exceeded expectations by approximately $20,000.00, chiefly due to increase in Life Memberships. The surplus for the year 1944 will be about $25,000.00, $22,000.00 of which is not available for use, being represented by Life Membership fees which are deposited in the Endowment Fund. The College operated during 1944 well within its budget; the Committee had reviewed budgets for 1945, showing total estimated income of $103,000.00 and expenditures of $89,270.00, leaving an anticipated surplus of $13,830.00.

By resolution, the proposed budgets for 1945 were approved, with certain minor additions for special purposes. Also by resolution, the following matters affecting finances were acted upon:

The suggestion from the American Physicians Art Association that the College offer prizes for the stimulation of painting of medical subjects, be politely declined; that the College contribute $5,000.00 toward the program of the War-Time Graduate Medical Meetings during 1945; that the College authorize completion of all necessary arrangements for the establishment and initiation as of January 1, 1945, of a pension system for full-time employees, in accordance with principles adopted at the preceding meeting of the Board, and that the Secretary General, Treasurer and Chairman of the Finance Committee constitute the Pension Committee, the Secretary General acting as Trustee.

Full and detailed statements of receipts and expenditures of the College for 1944, with estimates for November and December, as well as the detailed budgets proposed for 1945, were presented to the Regents for review, and were subsequently approved.

In closing his report, which was adopted as a whole, Dr. Pepper re-affirmed the Committee's satisfaction with the services of Drexel & Company, the financial counsel of the College, and on behalf of the Committee expressed appreciation of the efficiency of the Executive Secretary in all matters.

Dr. William D. Stroud, Treasurer, presented the following report:

"I am gratified to report that the financial condition of the College is excellent; that the income for 1944 will be approximately $20,000.00 in excess of that anticipated a year ago; that the College has operated within its budget for the current year; that the accounts of the College will be audited by a professional accountant at the end of the year. A more detailed report is not presented now because the Executive Secretary has already placed in your hands the analysis of income and expenditures for the year, and the Chairman of the Finance Committee has made an all-inclusive report. At the last meeting of the Board, we appropriated up to $1,000.00 to the National Council for the Prevention and Treatment of Rheumatic Fever. To date, the Council has not called for this amount. This is because the Council is attempting to raise a total of $100,000.00 before it begins its work.

"The market value of the investments of the College is $295,868.00, of which 47.3 per cent is in Bonds, 22.4 per cent in Preferred Stock and 27.7 per cent in Common Stocks. The cash income from these investments for the last year has been $10,781.00, a yield of 3.74 per cent."

Dr. Stroud, as Chairman of the House Committee, thereafter presented a report on the upkeep, maintenance and improvement of the Headquarters building and grounds, with a total expenditure of $6,092.03. The College continues to house the War-time Graduate Medical Meetings, furnishing them without charge room, heat, light and service.

Dr. Chauncey W. Dowden, Chairman of the Board of Governors, reported at length on the interim activities of that Board and read several letters from Governors concerning policies of the College. Several Governors had discussed the matter of making certification a prerequisite for Associateship, and the general attitude appeared to be unsatisfactory. Among the letters read was one from Surgeon General Thomas Parran, advocating recognition of competence in medicine in the Service as requisites for membership in the College, rather than the extension of certifying examinations.

At this point, the Board took up the consideration of holding an Annual Business Meeting and brief war session in the spring. By resolution, it was decided that these meetings be conducted in St. Louis, in connection with the Regional, War-Time Meeting under the general chairmanship of Dr. Ralph Kinsella, Governor for Missouri. It was suggested that the Regional, War-Time Meeting consist of one day of clinics

and one day of formal papers, that medical officers of the Armed Forces be invited and that one day be devoted to a combined executive session of the Board of Governors and Board of Regents, to the Annual Business Meeting for the transaction of formal business of the College and the election of Officers, Regents and Governors. Dr. Kinsella was appointed Chairman of Local Arrangements.

Subsequently, the dates of May 3–4 were selected for the scientific aspects of the meeting, and May 5 for the executive session of the Regents and Governors and the Annual Business Meeting.

The Committee on Credentials was authorized to hold a meeting about three weeks in advance of the annual meeting to review the credentials of candidates for membership.

Adjournment